

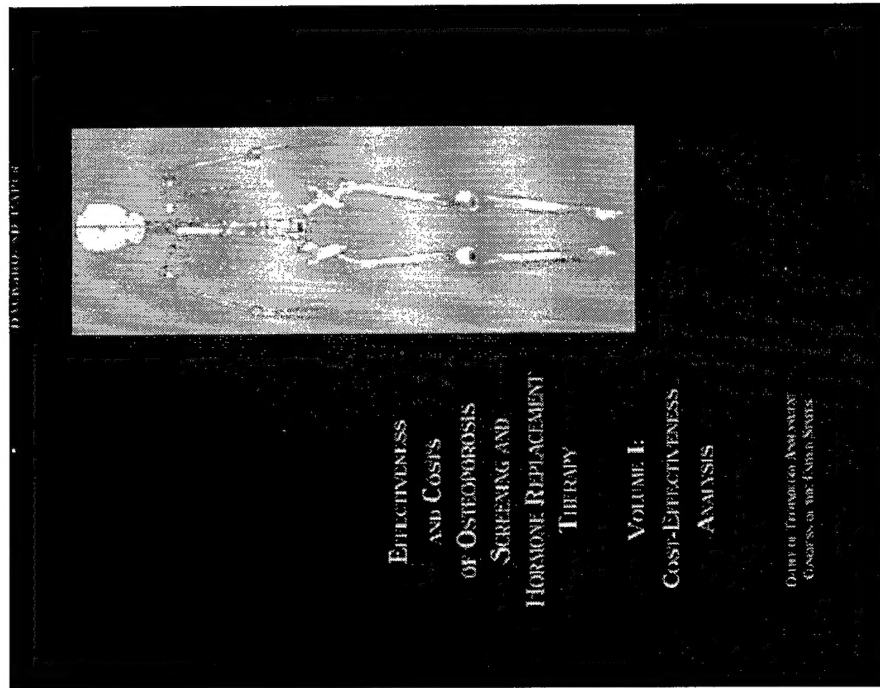
*Effectiveness and Costs of Osteoporosis  
Screening and Hormone Replacement  
Therapy, Vol. I: Cost-Effectiveness Analysis*

August 1995

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# Foreword

**M**enopause typically occurs in women around age 50. Accompanying this life event is a decline in estrogen levels and an increase in the rate of decline in women's bone density. This rapid bone loss increases women's subsequent risk of developing osteoporosis, a disease characterized by low bone density and increased bone fragility. Among the most serious consequences of osteoporosis is fracture of the hip, which may result in substantial morbidity, prolonged hospitalization, and death. Estrogen can prevent bone loss after menopause by replacing the body's own estrogen. Given the serious consequences of osteoporosis, some osteoporosis experts have recommended that women have their bone mineral density measured at the time of menopause and those with the lowest bone mineral density be offered *hormone replacement therapy*, comprising estrogen given alone or in combination with the hormone progestin.

This background paper, *Effectiveness and Costs of Osteoporosis Screening and Hormone Replacement Therapy*, assesses the medical benefits and costs of both screening and hormone replacement therapy. It is divided into two volumes. The first volume, *Cost-Effectiveness Analysis*, presents the results of a model that estimates the cost per year of life gained from osteoporosis screening and hormone replacement therapy in postmenopausal women. The second volume, *Evidence on Benefits, Risks, and Costs*, provides the basis for the assumptions about the costs and effects of screening and hormonal replacement therapy used in the cost-effectiveness model.

This background paper is one of three documents resulting from OTA's assessment of policy issues in the prevention and treatment of osteoporosis. This assessment was requested by the Senate Special Committee on Aging, Senator Charles Grassley and Senator John Glenn, and the House Select Committee on Aging, Representative Olympia J. Snowe, Representative Benjamin A. Gilman, and former Representatives Brian J. Donnelly, Thomas J. Downey, and Patricia F. Saiki. Two background papers in this series have been issued, both in July 1994: *Public Information about Osteoporosis: What's Available, What's Needed?*, and *Hip Fracture Outcomes in People Age Fifty and Over*.



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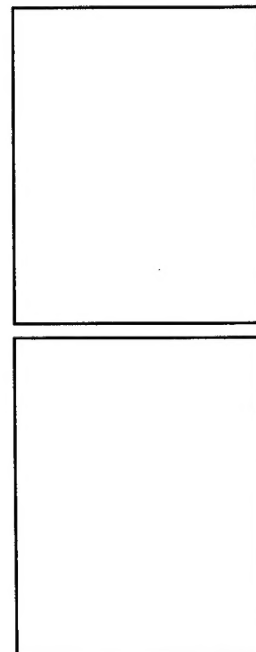
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# Summary of Findings

**T**his background paper assesses the costs and effectiveness of screening women for bone density once, at the time of menopause (age 50) or alternatively at age 65, and placing those with low bone density on long-term hormonal replacement therapy (HRT).

Based on a review of the literature, OTA made assumptions about the major adverse health events affected by HRT: hip fracture, coronary heart disease, breast cancer, endometrial cancer and gallbladder disease. The base-case assumptions represent OTA's judgments about the most likely level of effects. OTA also looked at the effect of best-case assumptions (those most favorable to osteoporosis screening and HRT) and worst-case assumptions (those least favorable to osteoporosis screening and HRT) on the estimated cost effectiveness of screening and HRT.

OTA's estimates include the costs (or savings) of hospital care, nursing home care, and other long-term care due to disease-related disabilities as well as the costs of screening and HRT. OTA did not include the cost of unpaid care provided by family and friends.

Because evidence on the quality of life associated with HRT and the diseases affected by it is scanty and even nonexistent for some conditions, OTA estimated HRT's impacts only on the length of life, not on its quality. Yet, HRT may have a major impact on quality of life through its short-term side effects and relief of menopausal symptoms and its long-term impact on fractures, heart disease, breast cancer, and endometrial cancer. Many elderly women with hip fractures, for example, never regain full function or independence. This summary identifies the conditions



## 2 Effectiveness and Costs of Osteoporosis Screening and Hormone Replacement Therapy

**TABLE A: Principal Effects of Hormone Replacement Therapy**

	ERT		PERT	
	Base case assumptions	Direction of effect <sup>a</sup>	Base case assumptions	Direction of effect <sup>a</sup>
Reduction in bone loss while on therapy	100%	+	100%	+
RR of heart disease while on therapy	0.5	+	0.8	+
RR of breast cancer after long-term therapy	1.35		1.35	—
RR of endometrial cancer after long-term therapy	7.0		1.0	0
RR of gallbladder disease while on therapy	2.5		2.5	—

<sup>a</sup>Indicates whether the base case assumption does (+) or does not (-) improve the cost-effectiveness ratios of the screening/treatment regimens

KEY: ERT = estrogen replacement therapy, PERT = progestin/estrogen replacement therapy, RR = relative risk

SOURCE Office of Technology Assessment, 1995

under which quality of life considerations could alter judgments about the most appropriate screening/HRT strategy.

HRT regimens consist either of estrogen given alone (ERT) or estrogen given in combination with a progestin (PERT). Evidence is strong that ERT retards the rate of bone loss and reduces the risk of hip fracture, but it also increases the incidence of endometrial cancer. Suggestive evidence also exists for a reduced risk of coronary heart disease and an elevated risk of breast cancer and gallbladder disease in women on ERT for extended periods of time. PERT eliminates the excess risk of endometrial cancer, but it may also reduce the heart disease benefits associated with ERT. OTA's base case assumptions regarding the impact of ERT and PERT on each disease are shown in table A.

OTA examined a number of screening/HRT strategies, defined by the age at which bone mineral density (BMD) measurement occurs, the BMD threshold for initiation of a course of long-term HRT, and the duration of therapy. The screening/HRT strategies examined are listed in table B.

OTA's cost-effectiveness analysis can be used to guide overall public health policy, including decisions about educational programs or payment for screening or HRT, but it is not intended to guide individual decisions regarding BMD screening or long-term HRT. Individual women's

risks of the various conditions and diseases affected by HRT vary, as do their assessments of the quality-of-life implications of various outcomes.

The findings of OTA's cost-effectiveness analysis are summarized below:

- Given base case assumptions, screening women for osteoporosis at menopause and placing those with low bone density on long-term ERT would deliver an additional year of life for about \$27,000, which is a reasonable cost per added year of life compared with many interventions currently paid for by public and private third-party payers.
- Given base case assumptions, placing all women on long-term ERT at menopause, without screening for bone density, would deliver an additional year of life for about the same amount, roughly \$23,000.
- Although the cost per added year of life is about the same for these two preventive strategies, their aggregate costs and benefits differ. The aggregate cost of the latter approach is higher than the former because more women are treated, and the aggregate benefits are also higher because more lives are saved (about 11,000 years of life per 100,000 women entered in the program vs. about 1,800 years of life per 100,000 women, respectively).

**TABLE B: BMD Screening/HRT Strategies Considered by OTA**

**Age at which BMD measurement occurs:**

- 50 years old
- 65 years old

**BMD threshold for initiating a course of therapy:**

- BMD 1 standard deviation below the mean
- BMD below the mean of the population
- Offer HRT to all women (no BMD screening)

**Duration of therapy:**

- 10 years
- 20 years
- 30 years
- 40 years

KEY: BMD = bone mineral density; HRT = hormone replacement therapy.

SOURCE Office of Technology Assessment, 1995.

- Regardless of the screening/treatment strategy chosen, the cost per added year of life declines dramatically with the duration of ERT, so that a lifelong course of therapy delivers the greatest benefit per dollar spent. Shorter durations of HRT—10 to 20 years—are less cost-effective than are longer treatment durations, largely because substantial medical benefits accrue only when women stay on the therapy into old age, when hip fractures and heart disease would rise dramatically. OTA's model suggests that 10 years of HRT is extremely costly regardless of whether or how HRT is targeted.
  - OTA's estimated cost-effectiveness ratios are most sensitive to assumptions about the effect of ERT on heart disease. In the base case, OTA assumed the existence of a substantial reduction in heart disease with ERT. This assumption may be incorrect because the evidence of heart disease benefits from ERT is based on observational studies, which may be biased. *If ERT has no heart disease benefit*, the cost per added year of life for all screening/ERT strategies would be high. In this circumstance, putting all women on a lifetime course of ERT would cost roughly \$450,000 per added year of life.
- Screening women for osteoporosis at menopause and placing those with low bone density on long-term ERT would cost less—roughly \$155,000 per added year of life—but it is substantially more costly per added year of life than are most preventive technologies currently accepted for Medicare payment.
- If ERT has no heart disease benefits, the quality-adjusted cost-effectiveness ratio of screening and long-term ERT for those with low bone density would depend on the improvement in quality of life from fewer fractures compared with the decline in quality of life from increased risks of breast and endometrial cancer. The impact on quality of life from fracture incidence reduction would occur relatively late in life, because most fractures occur in the very old, whereas the quality of life impacts of increased cancer incidence would occur earlier in life. Depending on the value people place on these impacts, the quality-adjusted cost-effectiveness ratio could be either higher or lower than the unadjusted cost-effectiveness ratio given above.
  - Current practice is to prescribe PERT for long-term therapy. Although PERT clearly eliminates the excess risk of endometrial cancer, it may also reduce the magnitude of heart disease benefits obtained from ERT. Clinical trials have demonstrated that the addition of progestins reverses some or all of ERT's favorable effects on lipoproteins. Under OTA's base case assumption that PERT has a small but significant effect on heart disease benefit of PERT, placing all women on long-term PERT would cost roughly \$71,000 per added year of life. Placing only those with low bone density on long-term PERT would cost about the same amount per added year of life.
  - If PERT has no heart disease benefit, the cost per added year of life is very high for *all* screening and treatment strategies. For example, the cost of putting all women on PERT would be about \$262,000 per added year of life. Quality-

#### 4 | Effectiveness and Costs of Osteoporosis Screening and Hormone Replacement Therapy

of-life adjustments could change this ratio, but the magnitude and direction of the change cannot be predicted with currently available evidence.

- OTA considered including the cost of vertebral and other fractures associated with osteoporosis in the analysis, and did not do so. Good estimates of the health care costs associated with these fractures are unavailable. As discussed in the report, the costs of wrist and vertebral fractures are very low in comparison with the costs of other adverse health conditions considered in this analysis. OTA therefore concluded that adding these costs would make no difference to the basic conclusions of the study.
- OTA's estimates of cost effectiveness assume complete compliance with HRT, which may be unrealistic. Studies have shown that long-term compliance with HRT is low, usually below 20 percent. The effect of incomplete compliance is to reduce the cost effectiveness of all screening/HRT regimens considered. For example, OTA found that, if 50 percent of women were to terminate ERT after only 10 years while the rest of the population remained on therapy for life, the cost per added year of life for this population as a whole would be \$73,000. Although new HRT regimens under development may have fewer undesirable side effects, their ultimate impact on compliance is unknown.
- Beginning HRT at older ages (e.g., 65 years of age) may be more cost-effective than beginning it at the time of menopause, but such a conclusion depends on extrapolating the range of cardiac benefits seen in women who begin HRT at menopause to women who begin therapy at older ages.
- Some osteoporosis experts propose that HRT should be targeted to those postmenopausal women at highest risk of fracture, as determined by BMD screening. There may be other methods, however, of selecting women who would gain the most from HRT. If HRT is effective for prevention of heart disease, for example, then it may be less costly and more effective to screen women for risk of heart disease and target HRT to those at highest risk. Furthermore, targeting HRT to those postmenopausal women with low bone density may discourage those women with low risk of fracture and high risk of heart disease from taking HRT.
- Bone density screening may increase uptake of and continuous compliance with HRT. The effectiveness of osteoporosis screening as a tool for improving compliance should be evaluated against other methods for improving compliance. In addition, the use of bone mass measurements in inducing other changes in lifestyle needs evaluation in comparison with other methods of inducing multiple lifestyle changes.
- OTA analyzed the cost effectiveness of a hypothetical drug to maintain bone density without any of the adverse or beneficial side effects associated with HRT. OTA assumed that such a drug would cost about \$250 per year (the annual cost of PERT today). Screening women for BMD and placing those with the lowest BMD levels on a targeted osteoporosis drug would cost approximately \$155,000 per added year of life. Adjusting this ratio for improvements in the quality of life due to reduction in the number of fractures would surely make such a drug more cost-effective depending on the value people place on these improvements.



# Cost-Effectiveness Analysis

**O**steoporosis is a disease characterized by low bone density and increased bone fragility, which reduce bone strength. As a contributing factor in fractures of the hip and other skeletal sites in older people, especially older women, osteoporosis takes a high toll in lost years of independent living and expenditures for health care. The major source of morbidity and mortality from osteoporosis arises from hip fractures. OTA estimates that total societal expenditures for hip fractures, not all osteoporosis-related, were \$5 billion in 1990 (132).

The search for ways to prevent osteoporosis and its consequences has led some experts to espouse screening for women around the age of menopause<sup>1</sup> (about 50 years of age) to identify those with low bone density who are at greater risk of fracture in subsequent years. Several technologies that measure bone density have been proposed as good screening tools for predicting future bone density and, hence, future risk of fractures. These available technologies include single photon absorptiometry (SPA), dual photon absorptiometry (DPA), dual energy x-ray absorptiometry (DEXA), and quantitative computed tomography (QCT). Proponents claim that such screening would allow clinicians and counselors to target preventive interventions to those at highest risk and thus offer improved health at a reasonable cost (94).



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<sup>1</sup> Menopause occurs naturally around age 50. Menopause is also a secondary consequence of surgical removal of the ovaries (bilateral oophorectomy) and of diseases causing premature failure of the ovaries.

## 6 | Effectiveness and Costs of Osteoporosis Screening and Hormone Replacement Therapy

The benefits of screening a population for high risk of future disease or adverse events depend on the availability of interventions that are effective in preventing those events. In the case of fractures associated with osteoporosis, many approaches to prevention have been proposed, including patient education, exercise, diet, dietary supplements, and architectural modifications of living quarters for those at risk. The evidence supporting the effectiveness of these alternatives is mixed (15, 22, 92).

Pharmacologic approaches have also been sought. Although research is currently underway on a number of compounds that might be effective in altering bone strength or the speed of bone loss as women age (53, 54, 77, 103, 111, 120), today only one medicine has been recognized by the U.S. Food and Drug Administration (FDA) as effective for the prevention of osteoporosis: the reproductive hormone estrogen.<sup>2</sup>

This background paper assesses the medical effectiveness, medical risks, and health care costs associated with screening women for bone density once, at age 50, or alternatively at age 65, and placing those with *low* bone density on long-term hormone replacement therapy (HRT).

Hormone replacement therapy refers to estrogen given alone or estrogen given sequentially or in combination with a progestin. In this report, HRT is a general term referring to either regimen, where a distinction is not necessary. When we are referring specifically to estrogen given alone, we call it estrogen replacement therapy (ERT). When a statement refers specifically to estrogen and progestin, it is called progestin/estrogen replacement therapy (PERT).

OTA estimated the cost effectiveness of several screening and treatment strategies by estimating the net health care cost per year of life gained from each strategy. In a cost-effectiveness analysis, the multiple health effects of screening and preven-

tive therapy are reduced to a single measure of effectiveness—the extra years of life, sometimes adjusted for differences in their quality, that are gained or lost as a result of the preventive strategy. The average cost of achieving a given increase in the length or quality of life is the cost-effectiveness ratio.

OTA developed a computer model of the costs, risks, and effectiveness of bone-density screening and HRT in women eligible for HRT. The model predicts the cost of bone-density screening and the incidence and costs of the major adverse health events associated with osteoporosis and HRT. These major events include hip fracture, heart attack, breast cancer, endometrial cancer and gall-bladder disease.

This background paper contains two volumes. This first volume describes the cost-effectiveness model, including the assumptions regarding the cost of screening and the effectiveness, risks, and costs associated with various HRT strategies. It presents OTA's findings regarding the cost effectiveness of alternative strategies for screening and HRT, and it analyzes the sensitivity of the findings to uncertainty about the assumptions. The final section compares the results of OTA's cost-effectiveness analysis with those of previous analyses and discusses the implications for health care policy.

The evidence on the benefits, risks and costs of HRT is summarized in Volume II of this report. That volume also gives the rationale for the structure and assumptions underlying the OTA cost-effectiveness model.

### MODELING THE COST EFFECTIVENESS OF OSTEOPOROSIS SCREENING/HRT STRATEGIES

OTA developed a computer simulation model of a hypothetical sample of women eligible for bone-density screening and HRT beginning at age 50

<sup>2</sup> Estrogen has been approved for marketing for the prevention and treatment of osteoporosis. Calcitonin has been approved for treatment of established osteoporosis, but its approval is qualified (106).

and ending either at death or at age 90, whichever comes first. For each woman in the sample, the model creates a fabricated health record that includes all relevant measures of each woman's health status (e.g., whether she has a condition or disease of interest) and health-related events (e.g., whether she is diagnosed with or dies from a condition or disease).<sup>3</sup>

Because many health states or events are governed by the laws of probability, the computer assigns health states and health-related events randomly according to predetermined probability distributions.<sup>4</sup> When a computer model determines what happens to each member of a hypothetical sample by figurative spins of a roulette wheel, it is referred to as a Monte Carlo simulation (73).

OTA's Monte Carlo simulation of a woman's health record begins with a random assignment of bone mineral density (BMD) at age 50 (or other starting age when appropriate). Preventive strategies correspond to specific BMD threshold values, i.e., BMD values below which HRT is initiated. Whether the woman is placed on HRT depends on whether her BMD falls below the specific threshold. Any woman whose measured BMD is below the BMD threshold is placed on HRT.

For those women placed on HRT, the probabilities of subsequent health-related events (e.g., hip fracture, heart attack, death, etc.) are adjusted to reflect the benefits or risks of hormone therapy. The computer then constructs each woman's health record year by year. In subsequent years, each woman is assigned to certain disease or death states with given probabilities depending on her age, current BMD, and whether she is currently on or ever has been placed on HRT. As each woman's health record is compiled, the computer keeps track of each health-related event, recording the age at which the event occurred and the health costs associated with it.

After the lifetime health record is constructed, a woman's total lifetime health care costs and number of years of life lived are computed. The estimated costs and effects incurred over time are discounted to their net present value in the year the program began.<sup>5</sup> Across all women in the sample, the mean lifetime health care cost and years of life lived are estimates of the average experience associated with the particular preventive strategy (or no prevention) in the population of women from which the simulated sample was drawn.

The effectiveness of a specific screening/HRT strategy (defined by a specific BMD threshold and duration of HRT) is estimated by computing the

<sup>3</sup> The computer simulation model is written in the Mumps computer language (Micronetics Standard Mumps (MSM) version 3.0 published by the Micronetics Design Corp.). Although MSM Mumps is a complete implementation of the ANSI standard implementation of Mumps, the OTA model makes use of MSM functions and utilities that may not be compatible with other implementations of Mumps. Copies of the program and documentation are available from the National Technical Information Service, Springfield, Virginia (NTIS # PB95-209805).

<sup>4</sup> Computers generate random numbers which can be used to determine whether some characteristic or event is assigned to a subject. When a program calls for a random number between 0 and 1, the computer generates a number which is equally likely to be anywhere in the interval between 0 and 1. This randomly generated number is then used to determine whether an event occurs. Suppose, for example, that 3 per 1,000 70-year-old women die from heart attacks. When a hypothetical woman in the simulation reaches the age of 70, the computer generates a random number with some value between 0 and 1. If the value of the random number is between 0 and 0.003, the health record is noted with the woman's death from heart attack, and the health record ends. If the random number generated by the computer is above 0.003, then no heart attack is recorded for that year and the woman continues to be subjected to various risks until she either dies from an assigned health-related event or the record closes at age 90.

<sup>5</sup> To compare outlays occurring in different time periods, they must each be discounted to their present value in the year of program initiation. The discounting of health effects as well as costs is necessary to ensure that programs whose benefits lie well in the future will not be found more cost-effective if postponed indefinitely (69). A discount rate of 5 percent per year was used to convert both years of life lived (effects) and costs in future years to their present value in the year the program begins. Although other discount rates may be used, a discount rate of 5 percent has become a commonly accepted value in health cost-effectiveness research. Use of a standard discount rate permits comparison of the results of this analysis with the results from the cost-effectiveness analyses of other health interventions.

difference in the net present value of years of life lived by the sample of women who undergo the strategy and the net present value of years of life lived in a hypothetical sample of women not subjected to screening and HRT. The net costs of the screening/HRT strategy are estimated as the difference in the net present value of lifetime health care costs incurred by the sample of women undergoing the strategy and the net present value of lifetime health care costs incurred by a sample of women not subjected to the strategy. The cost effectiveness of the strategy—the ratio of the difference in costs to the difference in years of life lived—is expressed as the net cost per year of life gained from the preventive strategy.<sup>6</sup>

The validity of this kind of model as a true picture of the expected effects and costs of various preventive strategies depends on the accuracy of the underlying assumptions about costs, risk of disease and death, the effects of therapy, etc. These assumptions are of two kinds: structural and parametric. Structural assumptions govern the shape of the relationship among the various measures of health status throughout a woman's life. For example, the model may assume that a woman's risk of breast cancer is altered by HRT only after she has been exposed to the therapy for a certain length of time. That the risk of breast cancer is altered only after a certain length of therapy is a structural assumption. Parametric assumptions, or *parameters*, describe the magnitude of the structural assumptions. Using the above example, the model may assume that the length of therapy required before the risk of breast cancer is elevated is 10 years. The assumption that 10 years is required is a parameter of the model.<sup>7</sup>

Uncertainty about both structural assumptions and specific parameters abounds in a model of the

complex set of diseases affected by bone-density screening and HRT. OTA made base case assumptions, representing our best estimate of the true structural relationship or parameter value. A standard technique for dealing with uncertainty about parameters is to perform *sensitivity analysis*, that is, to assess how sensitive estimates of cost and effectiveness are to changes in parameter values. OTA analyzed the sensitivity of the cost-effectiveness results to alternative values of specific parameters. In addition, we constructed best case and worst case sets of assumptions to test how simultaneously setting several uncertain parameters to their upper or lower limits would affect the estimated cost effectiveness of the intervention.

Assessing the sensitivity of results to changes in structural assumptions was not possible because it would require extensive reprogramming of the computer model. In the next section, we summarize all of the major structural and parametric assumptions (including the range of values considered in sensitivity analyses) in the OTA model of osteoporosis screening.

## ■ Structure and Assumptions of OTA's Osteoporosis Screening Model

Table 1 lists the potential effects and costs brought about by any particular osteoporosis screening and HRT regimen. Screening and subsequent HRT potentially affect both costs and health outcomes in both positive and negative ways.

The primary motive for bone-density screening (and long-term HRT in those with *low* bone density) is to reduce hip and other fractures that are more frequent in women with osteoporosis. By retarding the rate of decline in bone density after menopause, HRT helps protect women from fractures.

<sup>6</sup> The cost-effectiveness ratio is uninterpretable if it is negative. A negative cost-effectiveness ratio occurs either when the preventive strategy actually reduces health care costs without reducing effectiveness (i.e., cost saving), or when the preventive strategy results in a net increase in costs and reduction in health (i.e., a *dominated* strategy).

<sup>7</sup> The assumption about the magnitude of the alteration in breast cancer risk is also a parameter of the model.

TABLE 1: Effects and Costs of Osteoporosis Screening

Effects and costs of osteoporosis screening	Included in OTA's model?
<b>Effects</b>	
Longer life	
■ Treatment with HRT may reduce the risk of death from hip fracture	yes
● Treatment with HRT may reduce the risk of death from heart attack	yes
Shorter life	
● Treatment with HRT may increase the risk of death from breast cancer	yes
■ Treatment with HRT may increase the risk of death from endometrial cancer	yes
Higher quality of life	
● Treatment with HRT may reduce the pain and disability associated with hip fracture	no
■ Treatment with HRT may reduce risk of painful fractures of the spine and other sites	no
■ Treatment with HRT may reduce the pain and disability associated with coronary heart disease	no
■ Treatments with HRT relieve menopausal symptoms	no
Lower quality of life	
■ Treatment with HRT may increase the risk of pain and disability associated with breast cancer	no
■ Treatment with HRT may increase the risk of pain and disability associated with endometrial cancer	no
■ Treatment with HRT may increase the risk of pain and temporary disability associated with gallbladder disease	no
■ HRT itself may involve side effects, such as vaginal bleeding, that involve pain and discomfort.	no
<b>costs</b>	
Higher costs	
■ Screening for osteoporosis	yes
■ HRT (Including followup physician visits and procedures)	yes
■ Treatment of induced breast cancer	yes
■ Treatment of induced endometrial cancer	yes
● Treatment of induced gallbladder disease	yes
Lower costs	
● Prevention of hip fractures	yes
■ Prevention of other fractures	no
■ Prevention of coronary heart disease	yes

SOURCE Office of Technology Assessment, 1995

HRT has other consequences, however, some of which are good, others bad. The evidence is strong that prolonged use of ERT increases the incidence of endometrial cancer. PERT, on the other hand, appears to eliminate this increased risk.

More uncertain are the impacts of HRT on breast cancer and heart disease, which may also differ between ERT and PERT. OTA assessed the available evidence to arrive at a best estimate of these effects.

### ***Excluded Impacts***

OTA's model includes estimates of each potential category of cost and effect listed in table 1. These estimates include costs of hospitalization, nursing home care, and other long-term care due to disease-related disabilities. They do not include the costs of unpaid care provided by family or friends. The model also does not measure changes in the quality of life associated with HRT. Finally, it does not include changes in the incidence of fractures other than those of the hip. The reasons for these omissions from the model are considered below. The implications for the findings of the study of omitting these costs and effects are discussed in the concluding section.

### **Impacts on quality of life**

The consequences of bone-density screening and HRT for women's quality of life are not trivial. HRT affects the incidence of all kinds of fractures, and each kind of fracture involves some loss of function or enjoyment for a short or long duration. Box A summarizes the evidence on the effects of three of the most common kinds of osteoporosis-related fracture—hip, spine, and wrist—on short and long-run functional status. Hip fracture takes the greatest toll not only in terms of mortality (which is accounted for in OTA's model) but also in terms of long-term effects on ability to function independently.

Fractures are just one of the diseases or conditions affected by HRT. HRT also alters the incidence (and possibly severity) of heart disease, breast cancer, endometrial cancer, and gallbladder disease<sup>8</sup>. The impact of these diseases on functional status is also major. Data from the Framingham Heart Study suggest that in the aggregate, heart disease has a greater impact on functional limitations in the elderly than do hip fractures (50).

In five of seven activities of daily living, heart disease accounted for a greater percentage of the total disability discovered in elderly members of the Framingham cohort than did hip fracture (50).

Finally, HRT relieves symptoms of menopause, such as hot flashes, painful intercourse, and irritability. But HRT also has side effects such as periodic bleeding, depression, bloating, weight gain, and breast tenderness. Indeed, many women stop HRT when they find the side effects of the therapy intolerable (145).

The major problem with including quality-of-life impacts in a cost-effectiveness analysis is that people's preference for time spent in each possible state of health resulting from HRT must be compared with preferences for the same amount of time in a disease-free state. To compare changes in the length of life with changes in its quality, one would have to know how many years of healthy life consumers would be willing to give up to avoid a certain period spent in a specific disease state.<sup>9</sup> The value of a year of life lived with a specific outcome (say, a hip fracture) would be expressed as a quality-adjusted-life-year (QALY), a percentage of a year of healthy life. Although abundant information exists on the impact of hip fracture, heart disease, breast cancer, and other diseases on functional ability and other aspects of quality of life, the evidence is extremely sparse on how these impacts translate into QALYs.

In a study of QALYs in 67 patients who had survived a heart attack at some point in the previous 28 months, for example, the patients rated a year of life lived in their current state of health as equivalent on average to 0.88 years of life in excellent health (129). This valuation did not vary with time since the heart attack and was uncorrelated with changes in patients' functional status over time. Whether this value reflects those of people who

<sup>8</sup> In a cost-effectiveness analysis, the quality of life impacts of hip fracture would be discounted relative to cancers, given that hip fractures occur late in life and cancers much earlier (23).

<sup>9</sup> There are many theoretical and practical issues in measuring consumers' preferences for various states of health or disease. Whose preferences should be measured and when and how such preferences should be elicited are basic unresolved issues at present (133).

### BOX A: Impact of Fractures on Functional Limitations

Osteoporosis has been linked to an increase in the frequency of all kinds of fractures (14, 121). The three most common osteoporosis-related fractures—those of the wrist, spine, and hip—have unique profiles of effects on the severity and duration of functional limitations. Wrist fractures cause temporary partial disability and sometimes longer term loss of function. Spinal fractures are frequent in women with osteoporosis, but the majority do not cause symptoms severe enough to seek medical care. Hip fractures not only involve a short-term risk of mortality, but they also have a major impact on long-term function. Each of the three major kinds of fractures is discussed below.

**Wrist Fractures:** Wrist (Cones') fractures occur frequently in postmenopausal women. Like other fractures, the incidence of wrist fractures increases with age. For example, among white women in Rochester, Minnesota, in the 1970s the annual incidence of wrist fracture increased from 3.6 per 1,000 in women ages 50-54 to 6.9 per 1,000 in women 85 years of age or older (100). At any age, women with low bone mass have a higher incidence of wrist fractures (14, 56, 121).

Although wrist fractures do not cause death, they are painful, usually require one or more reductions, and need 4 to 6 weeks in a plaster cast to heal (65). An estimated 20 to 31 percent of wrist fractures are accompanied by short-term complications, including damage to the skin, fascia, tendons, and nerves (71).

Wrist fractures may also result in long-term functional impairment for a small percentage of patients. Full recovery generally takes a full year after fracture (35). In a Finnish study, 6 percent of patients had pain in the wrist area and 22 percent noted pain at the joint between the radius and ulna bones of the forearm at 6 months after the fracture (68). OTA found no empirical evidence on wrist function beyond the first year following fracture, but a small proportion of women can be expected to have permanent decline in wrist function.

**Vertebral Fractures:** Fractures of the spine (vertebra) are the most common kind of osteoporosis-related fracture. Estimating the relationship of bone mass to vertebral fractures is much more complex than with other fractures, in part because there is a lack of agreement among experts about the radiologic definition of vertebral fractures (14). On x-ray, vertebral fractures appear as vertebral deformities, rather than as a distinct fracture. The best evidence suggests that the risk of vertebral fractures increases two-fold with each standard deviation of bone mass below the mean BMD for a given age (14).

The prevalence of vertebral deformities in white women 50 years of age and older in Rochester, Minnesota, is estimated at 25.3 percent (87). (Black women have a much lower incidence of osteoporotic fractures.) Most vertebral fractures, however, do not cause symptoms and are never brought to clinical attention. In another study of almost 3,000 non-black women ages 65 to 70 recruited from the community, 60.6 percent had vertebral deformities, but only those with the most severe deformities (10.2 percent of the total population) had significantly higher levels of back pain, disability, or loss of height compared to women with no vertebral deformities (39). Because women with back pain might be more likely to volunteer for a study of osteoporosis, the prevalence of back pain in this group of women is likely to be higher than in the general population. Whereas 66 percent of women with no vertebral deformities had back pain at least rarely during the past year, 78 percent of women with severe deformities had back pain at least rarely; thus, about 12 percent more women with the most severe deformities were likely to experience back pain than those without any deformities. This suggests that under 1.3 percent of the total population of women 65 years of age and older suffers back pain as a consequence of severe vertebral deformities, most of which are due to osteoporosis (38). The same study found that women with the most severe vertebral deformities tended to have more problems with overall health, and did not rule out the possibility that other health conditions affecting pain and disability may



## 12 | Effectiveness and Costs of Osteoporosis Screening and Hormone Replacement Therapy

### BOX A: Cent'd.

also be correlated with vertebral fractures. Consequently, these estimates represent the maximum independent effect of vertebral fractures on pain and disability.

Of women with severe vertebral deformities, about 16.4 percent reported having much difficulty with one or more activities of daily living because of back pain within the past year, compared with 82 percent of women with no spinal deformities (39). This suggests that under 0.83 percent of the total population of elderly women had some decline in function as a result of severe vertebral deformities. Other studies have found impacts on functional abilities of about the same order of magnitude (124).

**Hip Fractures:** The risk that a 50-year-old woman will fracture her hip sometime during the rest of her life is about 16 percent (14). The risk of hip fracture is reversely related to bone mass at all ages above 50. (See appendix D )

Most of the recovery of functional abilities following a hip fracture occurs within the first 6 months after the fracture (62, 79). Three studies found that after 6 months, only about one-third of all elderly hip fracture patients regain their pre-fracture level of functioning (33, 62, 90).

A prospective study of a cohort of over 2,800 community-living elderly women traced the loss of function in 120 who sustained a hip fracture during the 6-year study period (81). Of the 120 women with hip fracture, 98 survived at least 6 months. Of the survivors, the percentages who could perform various functions, compared with those able to perform them at the beginning of the study, are shown below

	At baseline	6-month post-fracture
Dress independently	86%	49%
Transfer independently	90	32
Walk across room independently	75	15
Climb a flight of stairs	63	8
Walk 1/2 mile	41	6

Other studies of changes in functional abilities in older people also clearly illustrate the severe impact of a hip fracture. One study of change in functional abilities over a 6-year period among 356 older people in California found that a hip fracture led to significantly greater loss of functional abilities than any of the other acute medical conditions measured, including heart attack, stroke, and cancer (66). Another study of change in mobility over a 6-year period among 7,000 older people in three locations found that the risk for loss of mobility was two to five times greater for people who had a fracture than for people who did not (51). Moreover, the relative risk of loss of mobility was greater following a hip fracture than a heart attack, stroke, or cancer. In the aggregate, however, heart disease may have a greater effect on functional ability than hip fracture because of its much higher incidence in elderly women (50).<sup>1</sup>

<sup>1</sup>Based on estimates of the age-specific heart attack death rate and estimates of the ratio of fatal to nonfatal heart attacks, OTA estimates that the risk that a 50-year-old woman will have a heart attack sometime in her life is roughly 22 percent

have never had a heart attack is unknown, because there are no other similar studies.<sup>10</sup>

Two studies of QALYs in breast cancer have shown that the value of a year lived with breast

<sup>10</sup>Measuring time trade-offs in healthy people who lack direct experience with the disease under study requires that they be informed about the health states they are being asked to value. How such information is framed and how diseases are labeled can affect the values people assign to them (46).



cancer varies greatly depending on the stage of the disease at diagnosis, the prognosis for dying of breast cancer (versus other causes), and other information provided to respondents about the disease (8, 52). As is generally true in most QALY studies across diseases, women with breast cancer gave a higher value to living a year of life with the disease than did women without breast cancer. In an Australian study, women over 40 years of age rated a year with breast cancer with a favorable prognosis as equivalent to 0.79 healthy years of life and a year with breast cancer with a poor prognosis as equivalent to 0.3 healthy years of life (52).

Despite the abundant evidence that functional dependency increases after a hip fracture, there are no empirical estimates of QALYs associated with hip fracture.<sup>11</sup> It would be dangerous to speculate on such values based on what we know about functional status after a hip fracture, because people's willingness to pay to avoid a specific disease is not a straightforward function of such elements.

#### **Other omissions**

OTA did not estimate the savings in health care costs associated with reductions in wrist, vertebral, or other fractures resulting from long-term HRT because data on these costs are not available. Because these fractures rarely lead to hospitalization or nursing home placement, the cost of treating them is likely to be very low compared with the cost of hip fractures and other diseases affected by HRT. Thus, the effect of this omission on cost-effectiveness ratios is likely to be very small.

OTA also did not measure the costs of informal (unpaid) assistance provided by family and friends to patients with the conditions and diseases affected by HRT, because very little information is available on the amount of such care provided to patients of various ages with hip fractures, heart attacks, breast cancer, endometrial cancer, or gallbladder disease. The net effect of ignoring this dimension of cost on the cost effectiveness of various screening and HRT strategies is unknown, because the savings in such care from reductions in fractures and heart attacks are balanced to an unknown extent against extra costs from the increased incidence of breast cancer, endometrial cancer, and gallbladder disease. However, the value of these services may not be very important compared with the other health care costs of these diseases.<sup>12</sup>

#### ***Bone Density, HRT, and Hip Fracture***

The screening simulation model predicts, on the basis of each woman's measured BMD at age 50 (the typical age of onset of menopause) and her assigned HRT regimen, the probability of hip fracture in each subsequent year of life. Ideally, such a prediction would be based on the results of controlled clinical trials comparing hip fractures in women randomly assigned to HRT with those assigned a placebo or alternative therapy. Unfortunately, such studies do not exist.

Although several studies have consistently found a relationship between HRT and the incidence of hip fractures (see appendix B for a summary of all such studies), none of the existing studies of this relationship are randomized pro-

<sup>11</sup> Several osteoporosis cost-effectiveness studies have used estimates based on the subjective judgment of an individual or a small group of experts (23, 34, 127). Because such estimates have not been tested or validated, they serve only as exploratory studies.

<sup>12</sup> For example, one study of hip fracture patients age 65 and over who were treated in seven Maryland hospitals found that, two months after the fracture, 88 percent were receiving an average of 44 hours per week of informal care from family members and friends (67). However, before the hip fracture, 82 percent of the patients had received an average of 41 hours of informal care, so the difference (which was not statistically significant in the study) in the amount of family care given to hip fracture patients, particularly elderly patients, may not be great. A later report on this cohort found that direct nonmedical and informal care costs were lower six months or more after fracture than they were during the six months prior to the fracture (16). The investigators posited that this result may be due to chronic diseases in patients prior to hip fracture. Although OTA did not include the value of lost earnings, this value is also small, given that virtually all osteoporosis-related hip fractures occur in persons past the age of retirement.

spective clinical trials. All existing studies are observational studies, where treatment and control groups are not randomly assigned.<sup>13</sup> The limitations of such observational studies as definitive evidence of a causal relationship between an intervention and a clinical outcome are well known. More importantly, none of the existing studies of HRT and fracture examine a specific duration of HRT; rather, they typically report on the average experience of a sample of women whose HRT lasted for varying lengths of time. Thus, while the existing evidence relating HRT to a reduction in hip and other fractures is supportive of the existence of such effects, it provides little direct evidence on which to build a quantitative estimate of such effects.

In contrast, numerous prospective controlled studies are available on the impact of HRT on BMD. (See appendix C.) These studies show unequivocally that HRT reduces bone loss. For postmenopausal women treated with estrogen, bone loss initially ceases almost completely, and some studies show that bone mass may increase slightly and then show either maintenance or a gradual long-term decline. Long-term estrogen users have been shown to have significantly more bone mineral than matched controls at all sites measured (15). The reduction in the rate of bone loss continues as long as estrogens are taken (74, 75). Once estrogen therapy is discontinued, bone loss accel-

erates at a rate similar to that seen immediately after menopause in untreated women (25, 76).<sup>14</sup>

Because the evidence on the causal relationship between HRT and BMD is strong and consistent, OTA estimated the effectiveness of HRT on hip fracture in two steps. First, we estimated the impact of HRT on BMD at each age. Then we estimated the impact of BMD at each age on the probability of a hip fracture at each age. Thus, all effects of HRT on hip fracture were assumed to work through its effects on BMD.<sup>15</sup>

The general framework and specific parameters of a method to predict BMDs and hip fractures in women at each age between 50 and 90 were developed by Dennis Black under contract to OTA (14). The justification and details of the method are provided in appendix D. The method is described briefly below.

### Predicting BMDs

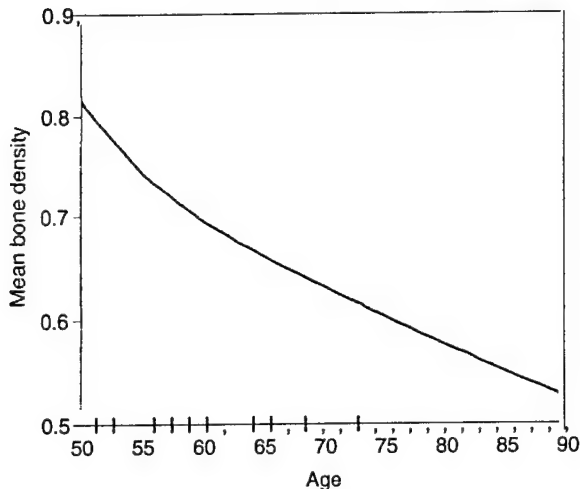
Data are available from a number of sources on the distribution (means, variances, and shape of the distribution) of BMDs, measured at the proximal radius (wrist), with single photon absorptiometry (SPA) at each age. (See appendix D.) Some data are also available on the correlation between a woman's measured BMD at age 50 and her BMD in subsequent years. On the basis of Black's review of available data and estimates, OTA as-

<sup>13</sup> Observational studies include both case-control and cohort studies. In case-control studies, the frequency of a suspected causative factor, such as estrogen use, is compared in a group of people who have a disease (cases) with those who do not (controls). If this factor is found with greater (or less) frequency in those with the disease, a causal association may be suspected. In cohort studies, the investigator begins with a group of subjects (the *cohort*), some or all of whom are exposed to a suspected causative factor, and follows this cohort over time for development of a disease. Comparison is made with a control group composed of unexposed members of the cohort (internal controls) or to subjects outside the cohort who are similar to members of the cohort, but who have not been exposed to the suspect factor (external controls).

<sup>14</sup> In the absence of hormone therapy, bone loss accelerates in the five years or so immediately following menopause and then proceeds more gradually in subsequent years (14, 20, 24, 56, 72, 74, 75, 82, 84, 85, 86, 88, 95, 115, 140).

<sup>15</sup> This assumption may either underestimate or overestimate the true number of hip fractures prevented by HRT. On the one hand, HRT may reduce hip fracture risk through mechanisms in addition to increasing bone mass. For example, HRT may reduce hip fractures by improving muscle strength and neuromuscular coordination, but this hypothesis is controversial (122). HRT may also prevent hip fractures by preventing chronic conditions, such as heart disease, which make people prone to falling. On the other hand, the effect of bone mass on hip fracture risk may be overstated because low bone mass may be correlated with other conditions predisposing people to hip fracture (30, 32, 42, 80, 107, 115). Browner and colleagues analyzed deaths occurring after hip and pelvis fractures and found that most of the increase in mortality is due to underlying conditions that are unlikely to be much affected by reductions in the incidence of these fractures (17).

**FIGURE 1: Mean Bone Mineral Density (gm/cm<sup>3</sup>) by Age Predicted in OTA's Osteoporosis Model**



SOURCE Office of Technology Assessment, 1995

sumed that at any age the BMD in a population of women follows a normal (bell-shaped) distribution. Each woman's BMD measured at the wrist at age 50 is sampled from a normal distribution with a mean BMD of 0.814 gm/cm<sup>3</sup> and a standard deviation of 0.1 gm/cm<sup>3</sup>. Although the mean BMD declines with age as shown in figure 1, the standard deviation is constant across ages. Subsequent BMDs are assigned on the basis of the starting BMD, age-specific correlation coefficients relating BMDs in each pair of years, and the mean and standard deviation of BMD in the population of women at each age. (See appendix D for details.)

#### Predicting the impact of HRT on BMD

HRT clearly retards bone loss and, according to most trials, may actually stop bone loss for the duration of therapy. Although the optimal dose of estrogen is uncertain, studies have consistently

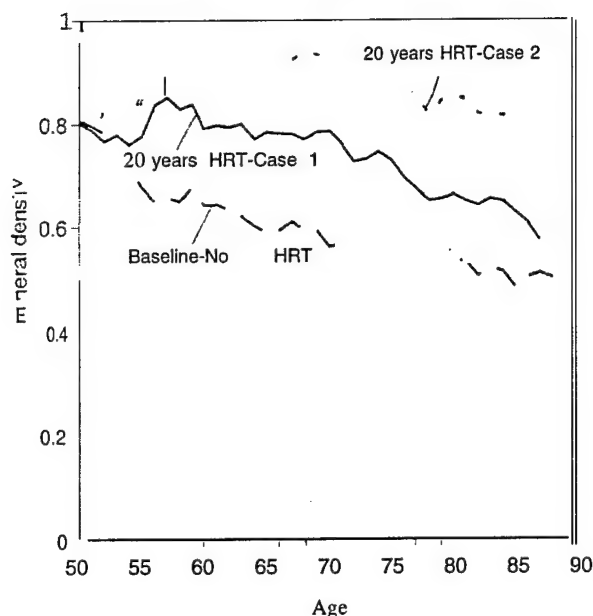
shown that doses in the range of 0.625 mg per day of conjugated estrogen or its equivalent are sufficient to protect bone mass during the course of therapy. (See appendix E for a discussion of the evidence on alternative HRT regimens.)

OTA assumed as a base case that the mean BMD in a sample of women on HRT would not change for the duration of therapy, although individual women's measured BMD values will vary randomly from year to year. "Thus, when a woman is placed on HRT because of a low initial BMD at age 50, her subsequent BMDs are assumed to be sampled from a population distribution whose mean and standard deviation do not change for the duration of therapy. (See appendix D.) When HRT ends, BMD is assumed to decline at the rate observed in women immediately following menopause.

The BMD parameters in OTA's model are based on bone-mass measurements taken by SPA in the wrist. Newer densitometry techniques, which measure bone mass at other body sites, may predict fracture with greater precision. For example, recent evidence suggests that DEXA measurements at the hip may predict the short-run risk of hip fracture more accurately than does SPA at the wrist (15). If such improved predictive accuracy were established over the long term, the effectiveness of screening would increase. (The cost effectiveness of screening would depend on the relative costs of different densitometry techniques.) Unfortunately, this possibility cannot be explored at present, because data are unavailable on either long-term prediction of hip fracture or the correlation of BMD measurements over time for any densitometry technique except for SPA at the wrist.

Figure 2 shows the simulated BMD trajectory of a woman whose initial BMD measured by SPA at the wrist is 0.806 mg/cm<sup>2</sup> and compares it with the simulated BMD trajectories of two women

"The relationship between a woman's BMD values in any two consecutive years depends on the strength of the correlation between BMD values measured over time. OTA's contractor estimated the correlation coefficients based on data provided by Hui (56, 57, 58). See appendix D for details.

**FIGURE 2: Bone Density in Three Simulated Cases**

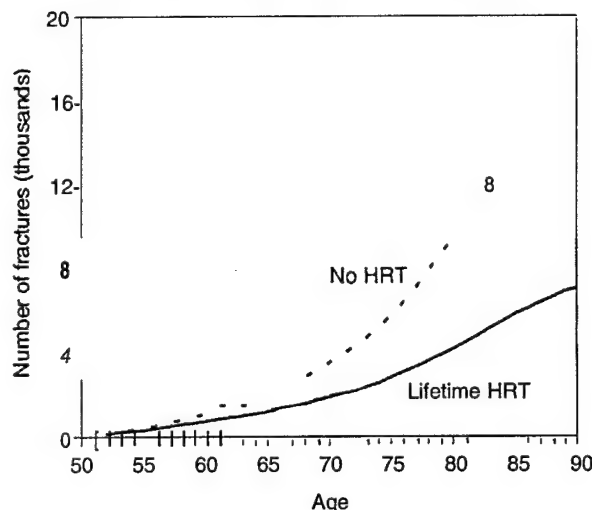
SOURCE: Office of Technology Assessment, 1995

whose initial BMD values are similar but who are placed on HRT for 20 years under the assumption that BMD halts bone loss for the duration of therapy. Figure 3 shows the cumulative lifetime hip fracture incidence predicted by the model for two simulated samples of 100,000 women. In one sample, none of the women is placed on therapy; in the other, all women are placed on HRT for the rest of their lives.

Because of uncertainty about the ability of HRT to preserve bone mass in the long term (39), OTA tested the sensitivity of the results to the assumption that HRT reduces the rate of bone loss by one half during the course of therapy.

#### Predicting hip fractures

The relationship between measured BMD in each year and the probability of hip fracture is based on data from the Study of Osteoporotic Fractures (SOF) on age-specific bone mass and hip fracture rates (31). The simulation model determines whether or not to assign a hip fracture to each sampled woman at each age from 50 through 90

**FIGURE 3: Cumulative Fractures per 100,000 Women Predicted in OTA's Osteoporosis Model**

SOURCE: Office of Technology Assessment, 1995

based on the probability of hip fracture, which is calculated as a function of both age and BMD. (See appendix D.)

#### Predicting hip fracture mortality

A hip fracture increases mortality, morbidity, and costs for the patient, her family, and society. In a separate background paper, OTA examined the evidence on the consequences of hip fracture (132). OTA concluded that hip fracture increases the risk of death in the year following fracture, but after the first year, the risk of death is no greater than that of the general population of women at each age. For the purposes of the model, therefore, OTA assumed that a woman with a hip fracture would have a probability of death in the subsequent year as shown in table 2. Those who survive beyond the first year are assumed to have a risk of death equal to that of the general population of women of the same age.

#### Breast Cancer and Hormone Replacement Therapy

HRT increases breast cancer risk by a small amount, if at all. Consequently, the evidence on

**TABLE 2: Mortality Rates Per 100 Women in the First Year After Fracture**

Age	Value	Age	Value
50	0.054	73	0.121
51	0.056	74	0.128
52	0.058	75	0.135
53	0.061	76	0.142
54	0.063	77	0.149
55	0.065	78	0.156
56	0.068	79	0.163
57	0.070	80	0.170
58	0.072	81	0.183
59	0.075	82	0.196
60	0.077	83	0.209
61	0.079	84	0.221
62	0.082	85	0.234
63	0.084	86	0.247
64	0.086	87	0.260
65	0.088	88	0.276
66	0.091	89	0.292
67	0.093	90	0.308
68	0.095	91	0.324
69	0.098	92	0.340
70	0.100	93	0.356
71	0.107	94	0.372
72	0.114		

SOURCE Office of Technology Assessment, 1995

the relationship is inconsistent: low risks are more difficult to detect and estimate than are high risks.

For purposes of this model, OTA assumed that the risk of breast cancer increases with HRT, but only after a patient has been exposed to HRT for a long period of time. In the base case, OTA assumed that women on HRT would have no increase in breast cancer risk until HRT therapy has continued for 10 years; in subsequent years, the relative risk of breast cancer in women on HRT compared with the general population is 1.35. OTA assumed treated women's risk of breast cancer

would remain elevated even after cessation of therapy. Because of the uncertainty surrounding these estimates, OTA investigated the sensitivity of the estimates of cost and effectiveness to a best case assumption that the relative risk of breast cancer is 1.0 and a worst case assumption that the relative risk is 2.0. HRT was assumed to have no effect on the stage distribution of detected breast cancers or on breast cancer prognosis. The basis for these assumptions is presented in appendix F, which summarizes the evidence on the relationship between HRT and breast cancer incidence.

Once a woman has breast cancer, the computer assigns an age of death based on age and stage at diagnosis. The probability of death as a function of time since diagnosis was constructed from the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) tumor registry data (108).<sup>17</sup> Because the assigned death age is based on data on deaths in breast cancer patients from all causes, once it is assigned, the death age overrides all other possible mortal events in the model. (That is, a woman cannot die earlier of most other causes.<sup>18</sup>)

OTA also assumed, based on a review of the epidemiologic evidence, that the addition of a progestin to estrogen replacement therapy does not reduce the risk of breast cancer associated with HRT.

### ***Endometrial Cancer and Hormone Replacement Therapy***

The impact of HRT on endometrial cancer differs widely between ERT and PERT. Endometrial cancer risk rises dramatically with the use of ERT and increases with the duration of ERT. After ERT is ended, however, evidence suggests that endometrial cancer risk rapidly returns to the pre-therapy level (63, 101, 117, 123). OTA assumed that the risk of endometrial cancer is elevated only with

<sup>17</sup> NCI provided OTA with unpublished data on 1-, 5-, 10-, and 15-year all-cause survival rates by age and stage at the time of detection.

<sup>18</sup> As explained later in this section, a death age is assigned if a woman contracts one of three conditions: breast cancer, endometrial cancer, or hip fracture. If a woman is assigned one of these conditions after having had a death age assigned for another, the original and new death ages are compared, and the youngest death age prevails.

current use of ERT and the risk increases with longer duration of ERT. For the first 10 years of therapy, the relative risk of endometrial cancer compared with women on HRT is assumed to be 3.5. Once ERT has exceeded 10 years in duration, the relative risk becomes 7.0. When ERT ceases, the relative risk returns to 1. The basis for these assumptions is presented in appendix G.

OTA tested the sensitivity of the results to changes in the relative risk of endometrial cancer. In the best case, OTA assumed a relative risk of 1 for short-term ERT and 2 for long-term ERT. In the worst case, OTA assumed a relative risk for short-term ERT of 7.5; and for long-term ERT of 15. (See appendix G.)

Although endometrial cancer risk is clearly elevated by ERT, women diagnosed with endometrial cancer while on ERT have much lower mortality rates than do those not on therapy at the time of diagnosis. The evidence suggests that women diagnosed with endometrial cancer while on ERT rarely die of it; rather, they are treated with a full hysterectomy, which is almost always curative (26, 28, 36, 37, 78, 113, 144).

The excellent prognosis for women diagnosed with endometrial cancer while on ERT is difficult to explain. It may be partly due to annual surveillance with endometrial biopsy, a standard precaution for women on long-term ERT. Since endometrial cancer is slow-growing, surveillance may be sufficient even with lower frequency in some women to detect endometrial cancers before they spread beyond the uterus. Some experts have suggested that the endometrial cancer induced by ERT is much more indolent than that occurring in other women (26, 28, 36, 37, 78, 113, 144). Re-

gardless of the reasons for the excellent prognosis in women with ERT-induced endometrial cancer, the most realistic assumption is that women diagnosed with endometrial cancer while on ERT have a negligible increase in mortality risk over those without endometrial cancer.<sup>19</sup> Thus, in this model, these women are subjected to hysterectomy, with its attendant costs, but they are not assigned a death age and remain at risk for death from unrelated causes in subsequent years.<sup>20</sup> Women diagnosed with endometrial cancer who are not currently on HRT are assigned a death age based on stage distribution and survival probabilities reported in the NCI SEER database.<sup>21</sup> (See appendix G for the rationale behind these assumptions.)

Today, PERT is the most frequently used HRT regimen in women with intact uteri, precisely because it eliminates the excess risk of endometrial cancer associated with ERT. It may even *reduce* the incidence of endometrial cancer compared with no therapy (40, 49, 152). OTA assumed that the relative risk of endometrial cancer in women on PERT is 1.0.

Just as the prognosis for endometrial cancers in women on ERT is more favorable than for endometrial cancers found in women not on therapy, the prognosis for endometrial cancer in women on PERT is also favorable (83). Although annual monitoring with endometrial biopsy is not routine in women on PERT, women on PERT are generally monitored more closely than others, and any incidents of unscheduled vaginal bleeding are evaluated with endometrial biopsies. OTA assumed that endometrial cancers found in women on PERT would not be fatal, requiring only pri-

<sup>19</sup> This is an underestimate of the true mortality associated with endometrial cancers in women on HRT, because some epidemiological studies have identified late stage cancers in women on HRT; in addition, early stage endometrial cancers are treated with a hysterectomy, and there is some mortality associated with any surgical procedure where anesthesia is used. Only a small number of deaths are associated with endometrial cancers in HRT users, so the consequences of this underestimate are small.

<sup>20</sup> Women who contract endometrial cancer while on therapy remain at risk for death from unrelated causes unless they have previously been assigned a death age because of breast cancer or hip fracture.

<sup>21</sup> It is possible for a woman not on therapy to contract both breast cancer and endometrial cancer. If a woman diagnosed with breast cancer and assigned a death age by the computer is later diagnosed with endometrial cancer, the breast cancer death age is compared with the endometrial death age, and the lower age is maintained as the assigned death age.



mary treatment (hysterectomy) and involving no excess mortality.<sup>22</sup>

As the results of OTA's analysis will demonstrate, one implication of the above assumptions about prognosis for women with endometrial cancer detected while on HRT is that endometrial cancer has very little effect on the principal outcome measure: years of life lived. Indeed, despite the high relative risk of endometrial cancer, the predicted years of life lived in women on ERT actually increase compared with the life expectancy of women not on therapy. This is because we assumed no women on ERT will die of endometrial cancer, whereas a certain percentage of the relatively smaller number of women not on therapy who get endometrial cancer would be predicted to die of the disease.<sup>23</sup>

The endometrial cancer assumptions also mean that years of life lost from endometrial cancer under any screening-HRT strategy will not differ according to the specific HRT regimen (ERT or PERT) adopted. The costs of treating endometrial cancer will differ between ERT and PERT, however, because many more women are detected with endometrial cancer under ERT than under PERT.

### **Gallstones and Hormone Replacement Therapy**

HRT taken by mouth has been linked to increased risk of gallstones, which require surgical removal (cholecystectomy) to relieve symptoms and prevent recurrence. Appendix H contains a review of the evidence on HRT and gallstones. Based on that review, OTA's model assumes a relative risk of gallstone disease while a woman is on HRT of 2.5. We also assume that the only consequence of gall-

stone disease is a cholecystectomy and that no excess mortality arises from this condition.<sup>24</sup>

### **Coronary Heart Disease (CHD) and Hormone Replacement Therapy**

Cardiovascular disease is the leading cause of death among U.S. women, surpassing the rates from cancer and other disease (18). Any change in the risk of cardiovascular disease due to HRT could profoundly alter the risk-benefit trade-offs of HRT. Most studies show that ERT reduces the risk of CHD in postmenopausal women, but the magnitude and post-therapy duration of the reduction in risk have not been established.<sup>25</sup> Even less information is available on the impact of PERT on CHD. Appendix I contains a review of the evidence on HRT and CHD.

It has been estimated that between 25 and 50 percent of the beneficial effect of estrogen on heart disease risk occurs through alteration of lipoprotein levels (12). Observational studies and randomized clinical trials have shown that estrogen reduces low-density lipoproteins (LDL, the *bad* cholesterol) and raises levels of high-density lipoproteins (HDL, the *good* cholesterol) (153). When progestins are added to the HRT regimen, however, these lipoprotein effects may be reduced. The rest of estrogen's beneficial effects on heart disease are mediated by other factors, such as estrogen's immediate effects on coronary artery vasospasm and clot formation. (See appendix I.)

Evidence on actual heart disease outcomes (e.g., fatal or nonfatal heart attacks, incidence of unstable angina, etc.) is weak, because although there are many studies of the relation between ERT and heart disease (see appendix I), virtually

<sup>22</sup> Not making this assumption for PERT, when it has been made for ERT, would lead to the anomalous result that PERT would cause more endometrial cancer deaths (and years of life lost) than would ERT.

<sup>23</sup> The OTA model is capable of analyzing different assumptions about stage and prognosis for endometrial cancer under HRT. We did not analyze other assumptions in this paper, because the evidence supporting the favorable prognosis is strong.

<sup>24</sup> This is an underestimate of the mortality associated with this procedure, as all surgical procedures requiring anesthesia carry a small risk of death. The surgical death rate associated with cholecystectomy is very low, however, so the consequences of this underestimate are small.

<sup>25</sup> HRT has been found *not* to increase the risk of stroke (59, 102, 104, 105, 114, 150).

none are randomized clinical trials. Results of 16 case-control studies, 16 cohort studies, and four cross-sectional studies, mostly of postmenopausal women on ERT, generally support the contention that the heart disease benefits are substantial—on the order of 20 to 80 percent reduction in risk during the therapy period. (See appendix I.) Several randomized trials have established a link between ERT and intermediate endpoints, such as short-term effects on cholesterol level. (See appendix I.)

Without randomized clinical trials linking ERT use to the incidence of or mortality from CHD, however, the very real possibility remains that these differences were found because patients who choose HRT are systematically *healthier* than or otherwise different from those who do not.<sup>26</sup>

Because observational studies and controlled clinical trials using intermediate endpoints suggest a CHD benefit from ERT, OTA assumed in the base case that the risk of heart attacks in women currently on ERT is 50 percent lower than the risk in women not on HRT. Once ERT is terminated, however, OTA assumed the risk reduction disappears and CHD incidence returns to that of the general population of women of the same age.<sup>27</sup> OTA further assumed that the ratio of fatal to nonfatal heart attacks would remain the same regardless of the risk level.<sup>28</sup>

Because of the importance of heart disease to both health outcomes and health care costs and the uncertainty concerning the benefits of ERT for

heart disease, OTA studied the impact on the results of changing the relative risks associated with ERT from 0.2 to 1.0.

As uncertain as the CHD benefits are in women on ERT, CHD benefits in women on PERT are even more uncertain. Few observational studies have been reported to date on the relationship, but observational studies and clinical trials of PERT's impact on lipoproteins suggest that the beneficial effect of estrogens is attenuated when progestins of the type and dose most commonly used in the United States are added to the HRT regimen. A randomized controlled clinical trial of HRT effects on CHD risk factors found that PERT eliminated about two-thirds to three-quarters of the increase in HDL cholesterol (153), the lipoprotein most closely linked to heart disease in women (13). Consequently, OTA assumed that the relative risk of a heart attack in women on PERT is 0.8, but we also examined the sensitivity of the results to assuming no benefit (i.e., a relative risk of 1.0.).

### Costs

OTA sought data on the health care costs of bone densitometry, HRT,<sup>29</sup> hip fracture, breast cancer, endometrial cancer, heart attacks, and gallbladder disease. When cost estimates were based on historical data, they were inflated by the medical expenditures component of the Consumer Price Index to 1993 constant dollars. The methods used to estimate each component of costs are described in detail in appendix J.

<sup>26</sup> The *healthy user bias* occurs when those who seek or use health services are in generally better health than those who do not and consequently have lower incidence of disease.

<sup>27</sup> The lipid hypothesis of estrogen protection against heart disease contradicts the empirical evidence on the shape of the observed association between estrogen use and heart disease risk (12, 109). The evidence suggests that estrogen protects only current users, and the degree of protection does not increase with longer durations of use. But the lipid hypothesis would predict that protective effects on the heart would come with long durations of estrogen use, because atherosclerotic plaques (fatty deposits) that block the arteries of the heart take years to develop.

<sup>28</sup> Epidemiological studies of HRT and heart disease incidence have found that the reductions in risk of fatal and nonfatal myocardial infarctions in HRT users are similar. See appendix I.

<sup>29</sup> The costs of HRT included annual physician visits, HRT prescriptions, and, for ERT, annual endometrial biopsies, as well as the cost of followup visits for problems associated with therapy.



TABLE 3: Summary of Assumptions in OTA's Osteoporosis Model

Assumptions about cost			
HRT annual treatment cost			
•(Estrogen only)		\$269	
■(Estrogen/progestin)		\$258	
BMD screening cost (SPA at wrist)		\$100	
Cost of fatal heart attack		\$14,470	
Cost of nonfatal heart attack		\$74,217	
Ratio of nonfatal to fatal heart attacks		2.6	
Cost of hip fracture		\$22,912	
Cost of cholecystectomy		\$11 160	
Discount rate, costs		0.05	
Discount rate, life years		0.05	
Lifetime cost of breast cancer			
■Localized		\$78,153 (age 50)-\$12,616 (age 90)*	
■Regional		\$67,274 (age 50)-\$1 5,837 (age 90)*	
■Distant		\$45,043 (age 50)-\$26,230 (age 90)*	
Lifetime cost of endometrial cancer			
■If on HRT		\$6,000	
■If not on HRT			
—Localized		\$15,702 (age 50)- \$8,635 (age90)*	
—Regional		<b>\$20203</b> (age 50)-\$1 3,418 (age 90)*	
—Distant		\$21,552 (age 50)-\$1 5,890 (age 90)*	
Assumptions about risks and benefits of HRT			
	Base case	Worst case	Best case
Relative risk of breast cancer			
•With less than 10 years' therapy	1.0	1.0	1.0
■After 10 or more years' therapy	1.35	2.0	1.0
Relative risk of endometrial cancer			
■While on HRT, with less than 10 years' therapy	3.5	7.5	1.0
■While on HRT, with 10 or more years' therapy	7.0	15.0	2.0
Relative risk of heart attack while on therapy	0.5	0.8	0.2
Relative risk of gallbladder disease, while on therapy	2.5	—	—
Impact of HRT on rate of bone loss, while on therapy	Stops loss of bone density	Reduces rate of loss by 50 percent	

\*Variable by age and stage

SOURCE Office of Technology Assessment, 1995

TABLE 4: Screening/HRT Strategies Examined by OTA

Therapy threshold	Duration of therapy (years)			
	10	20	30	40
<b>50 years old</b>				
1 standard deviation below mean BMD	X	X	X	X
Below mean BMD	X	X	X	X
Everyone on therapy	X	X	X	X
<b>65 years old</b>				
1 standard deviation below mean BMD		X		
Below mean BMD		X		
Everyone on therapy		X		

SOURCE Office of Technology Assessment, 1995

**Summary of Model Assumptions**

Table 3 summarizes the assumptions underlying the simulation model. The base case assumptions are best estimates of true parameter values. The best case assumptions are the most favorable to screening and HRT. The worst case assumptions are least favorable to screening.

**■ Screening/HRT Strategies Examined**

The costs and effects of an osteoporosis screening strategy depend on three elements of program design:

- the age at which BMD measurement occurs,
- the BMD threshold for initiation of a course of long-term HRT, and
- the duration of HRT therapy.

Table 4 contains a summary of the screening/HRT strategies tested by OTA.

**Age of BMD Screening**

OTA assumed that BMD screening would take place once at age 50. This screening age corresponds approximately to the average age at which natural menopause begins.

To examine the effect of delaying the initiation of screening and HRT, OTA performed additional

simulations in which BMD screening is initiated at age 65.

**BMD Threshold for HRT**

OTA examined alternative BMD thresholds for initiation of HRT:

- the lowest 16.7 percent of BMD values in the population (corresponding to a BMD threshold equal to 1 standard deviation below the mean for the hypothetical cohort at age 50),<sup>30</sup>
- the lowest 50 percent of measured BMD values in the population (corresponding to a BMD threshold value equal to the mean population BMD value), and
- all women regardless of BMD level at age 50.

In the third case—universal application of HRT to all women eligible for HRT—BMD measurement would be unnecessary. Therefore, in the third case, OTA assumed no screening would take place.

**Duration of HRT**

OTA considered only those preventive strategies involving long-term application of HRT—at least 10 years' duration. Although short-term HRT is

<sup>30</sup> A European osteoporosis consensus conference in 1993 defined low bone mass as BMD or bone mineral content (BMC) one standard deviation below the mean for the adult population (41 ).

**TABLE 5: Simulation Results: Baseline (No Intervention) in 15 Samples of 100,000 Women (\$ millions)**

Outcome	Mean (standard deviation)	Coefficient of variation (percent)	95 percent confidence interval <sup>a</sup>
Number of hip fractures	16,985 (1 04)	0.61 %	16,928-17,043
Total hip fracture costs			
■ undiscounted	\$389 (2.4)	0.61	379-391
■ discounted <sup>c</sup>	\$114 (0.9)	0.79	113-114
Number of breast cancers	10,135 (129)	1.28	10,064-10,207
Total lifetime breast cancer costs			510-517
■ undiscounted	\$513 (7.0)	1.36	509.5 -517.3
■ discounted	\$264 (3.8)	1.45	262-266
Number of endometrial cancers	2,378 (36)	1.51	2,358-2,398
Total lifetime endometrial cancer costs			
■ undiscounted	\$42 (0.7)	1.67	41-42
■ discounted	\$19 (0.4)	1.94	19-19
Number of fatal heart attacks	8,570 (49)	0.58	8,542-8,597
Total lifetime heart attack costs			
■ undiscounted	\$1,778 (10.2)	0.58	1,772-1,783
■ discounted	\$533 (3.5)	0.66	531-535
Number of gallbladder operations	12,576 (1 52)	1.21	12,492-12,660
Total lifetime gallbladder costs			
■ undiscounted	\$140 (1 .7)	1.21	139-141
■ discounted	\$67 (0.8)	1.26	66-67
Number of women alive at age 90	17,824 (1 00.2)	0.56	17,769-17,880
Total lifetime cost			
■ undiscounted	\$2,862 (1 2.2)	0.42	2,855-2,869
■ discounted	\$997 (5.9)	0.60	993- 1,000,0
Total years of life lived			
■ undiscounted	3,018,098 (2,576)	0.09	3,016,671-3,019,525
■ discounted	1,549,409 (846)	0.05	1,549,030-1,549,967

<sup>a</sup>The coefficient of variation is a relative measure of variation in a statistic. It is technically defined as the standard deviation of the statistic divided by the mean value of the statistic.

<sup>b</sup>The 95 percent confidence interval is the range of values of a statistic that contains the true value of the statistic with 95 percent probability. Confidence intervals were calculated using the appropriate t-distribution value with 14 degrees of freedom.

<sup>c</sup>Costs occurring in future years are discounted to their net present value at age 50 at 5 percent per year (for example, costs incurred at age 60 are multiplied by  $1/(1.05)^{10} = 0.614$  to arrive at their present value at age 50).

SOURCE: Office of Technology Assessment, 1995.

often indicated for relief of menopausal symptoms, the benefits of treatment for prevention of hip fracture tend to accrue only with longer use (43). OTA therefore examined the effects and costs of HRT maintained for 10, 20, 30 and 40 years. (A 40-year strategy is equivalent to placing a woman on a lifelong regimen of HRT.)

## RESULTS

### ■ Screening/HRT at age 50

OTA first ran the osteoporosis model under the base case set of assumptions with no preventive intervention. Fifteen separate samples of 100,000 women were used to estimate the mean and standard deviations of the major outcomes. Table 5

shows the estimated average values of these outcomes and measures of their variation for the *no intervention* strategy. The standard deviation across the 15 samples of every outcome measure was very low from 0.01 to 2 percent of the estimated mean value of the measure for all outcome measures.<sup>31</sup>

Most of the analyses were performed assuming that the HRT strategy being tested involves ERT. As noted above, adding progestin (PERT) to the strategy alters the incidence but not the outcome of endometrial cancer. The reduced incidence of endometrial cancer with PERT does translate into lower costs of endometrial cancer, but even when the risk is elevated seven-fold with ERT, endometrial cancer is relatively rare compared with the other diseases (breast cancer, hip fracture, and CHD) affected by HRT. Also, the net annual costs of ERT and PERT differ very little from one another. Thus, if nothing else were affected by the switch from ERT to PERT, the ratio of cost to effectiveness of any HRT strategy using PERT would be slightly lower than the ratio of cost to effectiveness of the same HRT strategy using ERT, and the cost effectiveness of ERT could be used as a rough guide for the cost effectiveness of PERT.

PERT may have a major impact on the cost effectiveness of HRT, however, because it potentially has a less beneficial effect on heart disease than ERT. This difference is reflected in a higher assumed relative risk of heart attack with PERT than with ERT. We therefore directly compared the cost effectiveness of several HRT strategies involving PERT with those of ERT to calibrate the two thera-

peutic approaches with one another. These comparisons permit summary statements about the relative cost effectiveness of alternative HRT strategies using PERT.

### **Outcomes with ERT: Base Case Assumptions**

Tables 6 through 10 show the results of sample simulations of 100,000 women under different ERT strategies for 50-year-old women. The lifetime incidence of hip fractures (table 6) declines from approximately 17 percent with no intervention, to about 7 percent when all women are placed on ERT for the rest of their lives. As expected, intermediate strategies in which fewer women are provided ERT, or they stay on ERT for shorter periods, reduce the lifetime incidence of hip fractures by lesser amounts.

The lifetime incidence of fatal heart attacks also decreases with intervention (table 7) from 8.5 per 100 with no therapy to 5.1 per 100 when everyone is placed on a lifelong regimen of ERT.<sup>32</sup> The gains from therapy accelerate in percentage terms as the duration of ERT increases. With everyone on therapy, for example, a 10-year ERT regimen reduces the incidence of fatal heart attacks by 5 percent. An additional 10-years of therapy reduces fatal heart attacks by another 6 percent. Adding 10 more years of therapy (to arrive at a 30-year ERT regimen) reduces fatal heart attacks by another 15 percent. Finally, going from 30 to 40 years of ERT means a further 23-percent reduction in heart attack deaths. This accelerating effect of ERT on cardiac death rates reflects the rising burden of CHD with age.

<sup>31</sup> The low variation across the 15 samples of size 100,000 suggests that samples of this size are sufficient to produce highly stable outcomes of the simulation model.

<sup>32</sup> Although the relative risk of acute myocardial infarction is assumed to be 0.5 while a woman is under therapy, the lifetime incidence does not decline by 50 percent with lifelong therapy, for two reasons. First, women on therapy have a much higher relative risk of endometrial cancer than do women not on therapy. The model assumes that once a woman is diagnosed with endometrial cancer she is removed from therapy, and the cardiac benefits of HRT are eliminated. Second, women diagnosed with breast cancer are also removed from therapy, and death rates from breast cancer increase with therapy.

**TABLE 6: Lifetime Incidence of Hip Fractures per 100,000 Women Under Different Osteoporosis prevention Strategies-Base Case Assumptions<sup>a</sup>(number of samples of 100,000)**

Duration of ERT	BMD threshold			
	Baseline: no screening, no ERT	Screen at 50 yrs old, ERT when BMD <1 STD below mean	Screen at 50 yrs old, ERT when BMD < mean	DO NOT screen, all women on ERT at 50 yrs old
No ERT	16,985 (15)	—		
10 years	—	15,978 (15)	14,374 (14)	12,865 (11)
20 years	—	15,268 (15)	12,374 (10)	9,801 (15)
30 years	—	14,796 (15)	11,229 (15)	7,833 (15)
40 years	—	14,653 (15)	10,871 (15)	7,184 (15)

<sup>a</sup>For base case assumptions, see table 3

KEY: BMD = bone mineral density, ERT = estrogen replacement therapy, STD = standard deviation

SOURCE: Office of Technology Assessment, 1995

**TABLE 7: Lifetime Incidence of Fatal Heart Attacks per 100,000 Women Under Different Osteoporosis Prevention Strategies-Base Case Assumptions (number of samples of 100,000)**

Duration of ERT	BMD threshold			
	Baseline: no screening, no ERT	Screen at 50 yrs old, ERT when BMD <1 STD below mean	Screen at 50 yrs old, ERT when BMD < mean	DO NOT screen, all women on ERT at 50 yrs old
No ERT	8,570			
10 years	—	8,549 (15)	8,449 (14)	8,211 (11)
20 years	—	8,496 (15)	8,214 (10)	7,784 (15)
30 years	—	8,298 (15)	7,652 (15)	6,680 (15)
40 years	—	8,054 (15)	6,888 (15)	5,149 (15)

<sup>a</sup>For base case assumptions, see table 3

KEY: BMD = bone mineral density, ERT = estrogen replacement therapy, STD = standard deviation,

SOURCE: Office of Technology Assessment, 1995

**TABLE 8: Lifetime Incidence of Breast Cancer per 100,000 Women Under Different Osteoporosis Prevention Strategies-Base Case Assumptions<sup>a</sup>(number of samples of 100,000)**

Duration of ERT	BMD threshold			
	Baseline: no screening, no ERT	Screen at 50 yrs old, ERT when BMD <1 STD below mean	Screen at 50 yrs old, ERT when BMD < mean	DO NOT screen, all women on ERT at 50 yrs old
No ERT	10,135 (15)	—	—	—
10 years	—	10,670 (15)	11,492 (14)	12,911 (11)
20 years	—	16,630 (15)	11,567 (10)	12,813 (15)
30 years	—	10,601 (15)	11,595 (15)	12,935 (15)
40 years	—	10,643 (15)	11,597 (15)	12,997 (15)

<sup>a</sup>For base case assumptions, see table 3

KEY: BMD = bone mineral density, ERT = estrogen replacement therapy, STD = standard deviation

SOURCE Office of Technology Assessment, 1995

**TABLE 9: Lifetime Incidence of Endometrial Cancer per 100,000 Women Under Different Osteoporosis Prevention Strategies-Base Case Assumptions<sup>a</sup>(number of samples of 100,000)**

Duration of ERT	BMD threshold			
	Baseline: no screening, no ERT	Screen at 50 yrs old, ERT when BMD <1 STD below mean	Screen at 50 yrs old, ERT when BMD < mean	DO NOT screen, all women on ERT at 50 yrs old
No ERT	2,378	—	—	—
10 years	—	2,589 (15)	3,092 (14)	3,826 (11)
20 years	—	3,332 (15)	5,360 (10)	8,399 (15)
30 years	—	3,896 (15)	7,235 (15)	12,073 (15)
40 years	—	4,136 (15)	7,997 (15)	13,558 (15)

<sup>a</sup>For base case assumptions, see table 3

KEY: BMD = bone mineral density, ERT = estrogen replacement therapy; STD = standard deviation

SOURCE Office of Technology Assessment, 1995

**TABLE 10: Lifetime Incidence of Gallbladder Disease per 100,000 Women Under Different osteoporosis Prevention Strategies-Base Case Assumptions<sup>a</sup>(number of samples of 100,000)**

Duration of ERT	BMD threshold			
	Baseline: no screening, no ERT	Screen at 50 yrs old, ERT when BMD <1 STD below mean	Screen at 50 yrs old, ERT when BMD < mean	DO NOT screen, all women on ERT at 50 yrs old
No ERT	12,576	—	—	—
10 years	—	13,233 (15)	14,585 (14)	16,559 (11)
20 years	—	14,024 (15)	17,112 (10)	21,649 (15)
30 years	—	14,708 (15)	19,054 (15)	25,488 (15)
40 years	—	14,932 (15)	19,819 (15)	26,974 (15)

<sup>a</sup>Incidence of gallbladder disease requiring cholecystectomy<sup>a</sup>For base case assumptions, see tables

KEY: BMD = bone mineral density, ERT = estrogen replacement therapy, STD = standard deviation

SOURCE Office of Technology Assessment, 1995

The lifetime incidence of breast cancer and endometrial cancer rises with ERT (tables 8 and 9). The incidence of breast cancer increases by 28 percent when all women are put on HRT for the remainder of their lives. Intermediate strategies have positive, but lower, effects on breast cancer incidence.

The lifetime incidence of gallbladder disease severe enough to require surgery increases from about 12.6 percent without intervention, to almost 27 percent with lifelong HRT for everyone (table 10).<sup>33</sup>

Tables 11 through 17 show the lifetime health care costs per 100,000 women of each cost component in the model: BMD measurement (screening), ERT, hip fracture, heart disease, breast cancer, endometrial cancer, and gallbladder disease. These tables present both the undiscounted and discounted costs of each component under the 12 screening/HRT strategies studied. Discounted costs are substantially lower than undiscounted costs in all categories except BMD measurement, because that is the only cost component fully incurred in the first year of the program (at age 50).

As expected, the costs of hip fractures and heart attacks decline as the number of people placed on ERT or the duration of ERT increases. Conversely, the costs of ERT itself and of treating breast cancer and gallbladder disease increase as the number of people on ERT or the duration of ERT increase. The costs of treating endometrial cancer also increase as the number of women placed on ERT or the duration of ERT increase, but the cost increase is very small. This result reflects the model's assumption that the treatment cost of endometrial cancer (\$6,000) diagnosed in a woman on HRT is substantially less than the treatment cost for a woman not on HRT at the time of diag-

nosis. (The lifetime cost of treating a localized endometrial cancer in a woman not on HRT ranges from \$8,635 to \$15,702, depending on the age at detection. (See appendix J.))

The net health care costs and years of life lived across all components of the model are shown in tables 18 and 19, respectively. Table 18 demonstrates that, compared with no intervention, any screening/ERT strategy increases lifetime health care costs. For example, placing all women on ERT for the remainder of their lives increases net lifetime undiscounted health care costs by 4.5 percent (from \$2.86 billion to \$2.99 billion per 100,000 women) and increases net lifetime discounted costs by 25 percent (\$1 billion to \$1.25 billion) compared with no intervention.

The net years of life gained from intervention are positive, although small (table 19). Placing all women on a lifelong course of ERT, for example, adds approximately 42,000 years of life to a cohort of 100,000 women, an average of approximately five extra months of life per woman.<sup>34</sup> When years of life lived are discounted to their present value at age 50, the gains in life extension are much more modest. ERT of 10 years' duration offers almost no net gain in discounted years of life; placing all women on a course of ERT for 10 years gains only 11,000 discounted years of life per 100,000 women, or slightly less than one additional month of life per woman on average.

### **Cost Effectiveness of ERT:**

#### **Base Case Assumptions**

If a preventive intervention both increases net health care costs and improves health outcomes, the ratio of incremental costs to incremental health effects is a useful measure of the improvements in the health outcomes of interest that each dollar buys on average.

<sup>33</sup> Although the relative risk of gallbladder disease is 2.5 with HRT, the actual incidence does not increase by that much because the model takes women off therapy if they are newly diagnosed with either breast or endometrial cancer.

<sup>34</sup> Of course, some women will die much earlier because of the adverse impacts of HRT (i.e., breast cancer), while others will die much later because they avoid fatal heart attacks or hip fractures.

## 28 I Effectiveness and Costs of Osteoporosis Screening and Hormone Replacement Therapy

**TABLE 11: Lifetime Cost of BMD Screening per 100,000 Women Under Different Osteoporosis Prevention Strategies—Base Case Assumptions\* (\$ millions)**

Duration of ERT	BMD threshold			
	Baseline: no screening, no ERT	Screen at 50 yrs old, ERT when BMD <1 STD below mean	Screen at 50 yrs old, ERT when BMD < mean	DO NOT screen, all women on ERT at 50 yrs old
<b>No ERT</b>				
undiscounted	\$0.0			
discounted <sup>b</sup>	0.0			
<b>10 years</b>				
undiscounted		\$10.0	\$10.0	\$0.0
discounted		10.0	10.0	0.0
<b>20 years</b>				
undiscounted		10.0	10.0	0.0
discounted		10.0	10.0	0.0
<b>30 years</b>				
undiscounted		10.0	10.0	0.0
discounted		10.0	10.0	0.0
<b>40 years</b>				
undiscounted		10.0	10.0	0.0
discounted		10.0	10.0	0.0

\*For base case assumptions see table 3

<sup>b</sup>Costs occurring in years subsequent to program initiation (at age 50) are discounted to their present value in the year of program initiation at a rate of 5 percent per annum

KEY: BMD = bone mineral density, ERT = estrogen replacement therapy, STD = standard deviation

SOURCE Office of Technology Assessment, 1995



**TABLE 12: Lifetime Cost of ERT per 100,000 Women Under Different Osteoporosis Prevention Strategies—Base Case Assumptions (\$ millions)**

Duration of ERT	BMD threshold			
	Baseline: no screening, no ERT	Screen at 50 yrs old, ERT when BMD <1 STD below mean	Screen at 50 yrs old, ERT when BMD < mean	DO NOT screen, all women on ERT at 50 yrs old
No ERT				
undiscounted	\$0.0		—	—
discounted*	0.0	—	—	
10 years				
undiscounted	—	\$41,3	\$129,8	\$259.8
discounted	—	33.6	105.6	211,4
20 years				
undiscounted	—	76,5	241,6	483,2
discounted		51.2	161,8	323.6
30 years				
undiscounted	—	102,8	323.3	646.4
discounted	—	59.5	187,2	374.3
40 years				
undiscounted	—	116.3	366.1	733.2
discounted		62.1	195,4	391.2

\* Costs occurring in years subsequent to program initiation (at age 50) are discounted to their present value in the year of program initiation at a rate of 5 percent per annum

KEY: BMD = bone mineral density, ERT = estrogen replacement therapy, STD = standard deviation

SOURCE Office of Technology Assessment, 1995

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**TABLE 13: Lifetime Cost of Treating Hip Fractures per 100,000 Women Under Different Osteoporosis Prevention Strategies-Base Case Assumptions (\$ millions)**

Duration of ERT	BMD threshold			
	Baseline: no screening, no ERT	Screen at 50 yrs old, ERT when BMD <1 STD below mean	Screen at 50 yrs old, ERT when BMD < mean	DO NOT screen, all women on ERT at 50 yrs old
<b>No ERT</b>				
undiscounted	\$389.2			
discounted*	113.6			
<b>10 years</b>				
undiscounted	—	\$366.1	\$329.3	\$294.8
discounted	—	106.2	94.9	84.2
<b>20 years</b>				
undiscounted		349.8	283.5	224.6
discounted		101.9	82.6	65.6
<b>30 years</b>				
undiscounted	—	339.0	257.3	179.5
discounted		99.5	76.8	55.7
<b>40 years</b>				
undiscounted	—	335.7	249.1	164.6
discounted		98.9	75.3	53.2

\*Costs occurring in years subsequent to program initiation (at age 50) are discounted to their present value in the year of program initiation at a rate of 5 percent per annum

KEY: BMD = bone mineral density, ERT = estrogen replacement therapy, STD = standard deviation

SOURCE Office of Technology Assessment, 1995

**TABLE 14: Lifetime Cost of Heart Attacks per 100,000 Women Under Different Osteoporosis Prevention Strategies—Base Case Assumptions (\$ millions)**

Duration of ERT	BMD threshold			
	Baseline: no screening, no ERT	Screen at 50 yrs old, ERT when BMD <1 STD below mean	Screen at 50 yrs old, ERT when BMD < mean	DO NOT screen, all women on ERT at 50 yrs old
<b>No ERT</b>				
undiscounted	\$1,777.6			
discounted*	533.0			
10 years				
undiscounted		\$1,773.4	\$1,752.6	\$1,703.3
discounted	—	530.7	516.4	493.0
20 years				
undiscounted		1,762.3	1,703.8	1,614.7
discounted		521.6	488.3	439.7
30 years				
undiscounted	—	1,721.3	1,587.3	1,385.6
discounted		508.3	453.1	367.5
40 years				
undiscounted		1,670.7	1,428.9	1,068.1
discounted	—	499.5	422.5	307.6

\*Costs occurring in years subsequent to program initiation (at age 50) are discounted to their present value in the year of program initiation at a rate of 5 percent per annum

KEY: BMD = bone mineral density, ERT = estrogen replacement therapy, STD = standard deviation.

SOURCE Office of Technology Assessment, 1995

## 32 I Effectiveness and Costs of Osteoporosis Screening and Hormone Replacement Therapy

**TABLE 15: Lifetime Cost of Endometrial Cancer per 100,000 Women Under Different Osteoporosis Prevention Strategies-Base Case Assumptions (\$ millions)**

Duration of ERT	BMD threshold			
	Baseline: no screening, no ERT	Screen at 50 yrs old, ERT when BMD <1 STD below mean	Screen at 50 yrs old, ERT when BMD < mean	DO NOT screen, all women on ERT at 50 yrs old
<b>No ERT</b>				
-undiscounted	\$41,5	—	—	—
discounted*	19,2	—	—	—
<b>10 years</b>				
undiscounted	—	\$41,7	\$42,7	\$43,7
discounted	—	19,3	20,1	21,0
<b>20 years</b>				
undiscounted	—	44,6	51,0	60,7
discounted	—	20,9	24,3	29,5
<b>30 years</b>				
undiscounted	—	46,8	58,7	75,9
discounted	—	21,5	26,7	34,4
<b>40 years</b>				
undiscounted	—	47,8	62,3	82,5
discounted	—	21,7	27,5	35,7

\*Costs occurring in years subsequent to program initiation (at age 50) are discounted to their present value in the year of program initiation at a rate of 5 percent per annum.

KEY: BMD = bone mineral density; ERT = estrogen replacement therapy; STD = standard deviation

SOURCE: Office of Technology Assessment, 1995

**TABLE 16: Lifetime Cost of Breast Cancer per 100,000 Women Under Different Osteoporosis Prevention Strategies-Base Case Assumptions (\$ millions)**

Duration of ERT	BMD threshold			DO NOT screen, all women on ERT at 50 yrs old
	Baseline: no screening, no ERT	Screen at 50 yrs old, ERT when BMD <1 STD below mean	Screen at 50 yrs old, ERT when BMD < mean	
<b>No ERT</b>				
undiscounted	\$513,4	—	—	—
discounted*	264,0			
<b>10 years</b>				
undiscounted	—	\$539.1	\$577,5	\$644,4
discounted		275,2	290,5	317,3
<b>20 years</b>				
undiscounted	—	537,2	579,5	638,4
discounted	—	274,1	289,6	314,0
<b>30 years</b>				
undiscounted		535,2	581,4	642,8
discounted	—	272,7	291,4	315,1
<b>40 years</b>				
undiscounted	—	537,7	580,2	644,1
discounted	—	274,4	290,1	315,5

\*Costs occurring in years subsequent to program initiation (at age 50) are discounted to their present value in the year of program initiation at a rate of 5 percent per annum

KEY: BMD = bone mineral density, ERT = estrogen replacement therapy, STD = standard deviation

SOURCE Office of Technology Assessment, 1995

### 34 I Effectiveness and Costs of Osteoporosis Screening and Hormone Replacement Therapy

**TABLE 17: Lifetime Cost of Gallbladder Disease per 100,000 Women Under Different Osteoporosis Prevention Strategies—Base Case Assumptions (\$ millions)**

Duration of ERT	BMD threshold			
	Baseline: no screening, no ERT	Screen at 50 yrs old, ERT when BMD <1 STD below mean	Screen at 50 yrs old, ERT when BMD < mean	DO NOT screen, all women on ERT at 50 yrs old
No ERT				
undiscounted	\$140.4	—	—	—
discounted*	66.9	—	—	—
10 years				
undiscounted	—	\$147.7	\$162.8	\$184.8
discounted	—	73.0	85.5	104.3
20 years				
undiscounted	—	156.5	191.0	241.6
discounted	—	77.5	100.1	133.3
30 years				
undiscounted	—	164.1	212.6	284.4
discounted	—	80.0	107.0	146.9
40 years				
undiscounted	—	166.6	221.2	301.0
discounted	—	80.7	108.8	150.4

\*Costs occurring in years subsequent to program initiation (at age 50) are discounted to their present value in the year of program initiation at a rate of 5 percent per annum

KEY: BMD = bone mineral density, ERT = estrogen replacement therapy, STD = standard deviation

SOURCE Office of Technology Assessment, 1995

**TABLE 18: Total Lifetime Cost per 100,000 Women of Different Osteoporosis Prevention Strategies (\$ millions)**

Duration of ERT	BMD threshold			
	Baseline: no screening, no ERT	Screen at 50 yrs old, ERT when BMD <1 STD below mean	Screen at 50 yrs old, ERT when BMD < mean	DO NOT screen, all women on ERT at 50 yrs old
No ERT				
undiscounted	\$2,862.1	—	—	—
discounted*	996.7			
10 years				
undiscounted		\$2,919.2	\$3,004.7	\$3,130.8
discounted	—	1,048.0	1,122.8	1,231.3
20 years				
undiscounted		2,936.9	3,060.4	3,263.1
discounted	—	1,057.2	1,156.6	1,305.7
30 years				
undiscounted		2,919.2	3,030.6	3,214.5
discounted	—	1,051.6	1,152.2	1,293.8
40 years				
undiscounted		2,884.8	2,917.7	2,993.6
discounted		1,047.2	1,129.6	1,253.6

\*Costs occurring in years subsequent to program initiation (at age 50) are discounted to their present value in the year of program initiation at a rate of 5 percent per annum

KEY: BMD = bone mineral density, ERT = estrogen replacement therapy, STD = standard deviation

SOURCE: Office of Technology Assessment, 1995

## 36 I Effectiveness and Costs of Osteoporosis Screening and Hormone Replacement Therapy

**TABLE 19: Total Number of Years of Life Lived per 100,000 Women Under Different Osteoporosis Prevention Strategies-Base Case Assumptions (thousands of years)**

Duration of ERT	BMD threshold			
	Baseline: no screening, no ERT	Screen at 50 yrs old, ERT when BMD <1 STD below mean	Screen at 50 yrs old, ERT when BMD < mean	DO NOT screen, all women on ERT at 50 yrs old
<b>No ERT</b>				
undiscounted	3,018.1	—	—	—
discounted*	1,549.5			
<b>10 years</b>				
undiscounted		3,018.5	3,020.2	3,021.5
discounted	—	1,549.8	1,550.4	1,551.4
<b>20 years</b>				
undiscounted	—	3,021.5	3,029.6	3,038.5
discounted	—	1,550.6	1,553.2	1,556.3
<b>30 years</b>				
undiscounted		3,025.1	3,036.9	3,052.4
discounted		1,551.4	1,554.8	1,559.1
<b>40 years</b>				
undiscounted	—	3,025.4	3,040.8	3,060.6
discounted		1,551.3	1,555.4	1,560.5

\*Years of life lived subsequent to program initiation (at age 50) are discounted to their present value in the year of program initiation at a rate of 5 percent per annum

KEY: BMD = bone mineral density, ERT = estrogen replacement therapy, STD = standard deviation

SOURCE Office of Technology Assessment, 1995



**TABLE 20: Cost Per Added Year of Life for 12 Osteoporosis Prevention Strategies—  
Base Case Assumptions (95% confidence interval)\***

BMD screening threshold	Number of years on ERT			
	10 years	20 years	30 years	40 years
1 S.D. below mean	\$151,392 (\$45,783-Undefined)	\$53,610 (\$31,432-\$165,262)	\$28,257 (\$19,777-\$47,240)	\$27,486 (\$18,865-\$47,815)
Below the mean	\$134,644 (\$73,364-\$758,436)	\$42,724 (\$34,606-\$55,524)	\$29,357 (\$25,490-\$34,484)	\$22,431 (\$19,687-\$25,954)
Everyone on therapy	\$126,876 (\$87,643-\$228,472)	\$45,761 (\$41,061-\$51,633)	\$31,059 (\$28,700-\$33,815)	\$23,334 (\$21,744-\$25,151)

\*Confidence Intervals computed based on Fieller's Theorem as cited in A.R. Willan and B.J. O'Brien, "Cost-Effectiveness Ratios in Clinical Trials From Deterministic to Stochastic Models," presented at the American Statistical Association meeting, Toronto, Canada, August 1994

KEY: ERT = estrogen replacement therapy

SOURCE Office of Technology Assessment, 1995

Table 20 contains the ratios of cost to years of life gained for each of the 12 osteoporosis prevention strategies under study. Regardless of the BMD threshold for ERT, the cost per added year of life declines dramatically with the duration of ERT. Forty years of ERT (a lifelong course) delivers an additional year of life for between \$22,000 and \$27,000 depending on the number of women placed on therapy.

The components of the cost effectiveness ratio (cost and years of life lived) were estimated from simulated samples of hypothetical women subjected to either a given preventive strategy or no intervention. The 95-percent confidence intervals for these components were very narrow. (See table 5 above.) Although the confidence intervals for the underlying components of the cost effectiveness ratio are very narrow, the cost effectiveness ratio is based on differences in costs and outcomes, which vary more widely. And because the net effects (years of life gained) are very small in

relation to the added costs (tens of thousands of years of life gained versus hundreds of millions additional dollars in costs), the ratio of net added costs to net effects has even greater variability.

No exact method exists for determining the confidence interval for a ratio of random variables such as the cost-effectiveness ratio (97, 148). OTA estimated the 95-percent confidence intervals for the cost-effectiveness ratios using two approximation methods recently reported in the literature.<sup>35</sup> Table 20 shows the approximate 95-percent confidence intervals for the cost-effectiveness ratio of each strategy under study.

The approximate confidence intervals for the cost-effectiveness ratio of strategies involving only 10 years of therapy are very wide. These results are to be expected given the low number of years of life gained under these strategies (table 18 above).<sup>36</sup> Thus, not only are the mean cost-effectiveness ratios associated with the shortest ERT

<sup>35</sup>One method, referred to as Taylor's Approximation (7), is useful when the estimate of net effectiveness is positive and statistically significant (148, 149). When effectiveness is near zero, a more exact method based on Fieller's Theorem should be used (149). OTA estimated the confidence intervals in table 20 and in selected cases (as noted) in tables 21 through 26 using Fieller's method. All other confidence intervals were estimated using Taylor Approximation.

<sup>36</sup>When the value of the denominator is low relative to the numerator, small changes in the denominator make for very large changes in the ratio.

**TABLE 21: Cost Per Added Year of Life for Two Osteoporosis Prevention Strategies'  
Best- and Worst-Case Assumptions About Relative Risks of Coronary Heart Disease  
Everyone on Therapy  
(95% confidence interval)**

	Number of years on ERT	
	20 years	40 years
Base case assumptions	\$45,761 (\$41,061-\$51,633)*	\$23,334 (\$21,744-\$25,151)*
Best case assumptions—CHD	\$28,431 (\$25,218-\$31,643)	\$7,153 (\$6,703-\$7,604)
Worst case assumptions—CHD	\$118,196 (\$83,162-\$203,109)*	\$78,860 (\$57,962-\$99,758)

\* All women are placed on therapy for either 20 or 40 years

\* Confidence Intervals computed based on Fieller's Theorem as cited in A.R. Willan and B.J. O'Brien, "Cost-Effectiveness Ratios in Clinical Trials From Deterministic to Stochastic Models," presented at the American Statistical Association meeting, Toronto, Canada August 1994

KEY: CHD = coronary heart disease

SOURCE Office of Technology Assessment, 1995

duration much higher than those of all other strategies, but the wide confidence intervals suggest that the true ratio may be very different from the estimate.

Together, these results imply that if a woman is to be placed on ERT, a lifelong course of therapy delivers the greatest benefit per dollar spent. Whether all women should be placed on therapy, or whether the ERT decision should be based on a BMD measurement at age 50, is more debatable. The cost-effectiveness ratios for the three 40-year ERT strategies are very close and are not significantly different from one another.

The estimated additional discounted lifetime cost of each BMD measurement strategy compared with no intervention rises as the number of women placed on therapy increases. The lifetime cost ranges from \$50 million per 100,000 when the 16 percent of women with the lowest measured BMD values are placed on HRT to \$257 million per 100,000 women when no BMD screening takes place and all women are placed on therapy. But the net measured health benefits also rise as the proportion of women on therapy increases. Placing women on ERT whose measured BMDs lie in the lowest 16 percent of the population delivers about 1,800 additional discounted

years of life per 100,000 screened women, while placing all women on ERT delivers 11,000 years of life per 100,000 women.

### ***Sensitivity Analyses with ERT***

OTA tested the effects of varying key parameters individually and together on the results of the cost-effectiveness analysis of screening/ERT strategies. The critical assumptions subjected to a sensitivity analysis were:

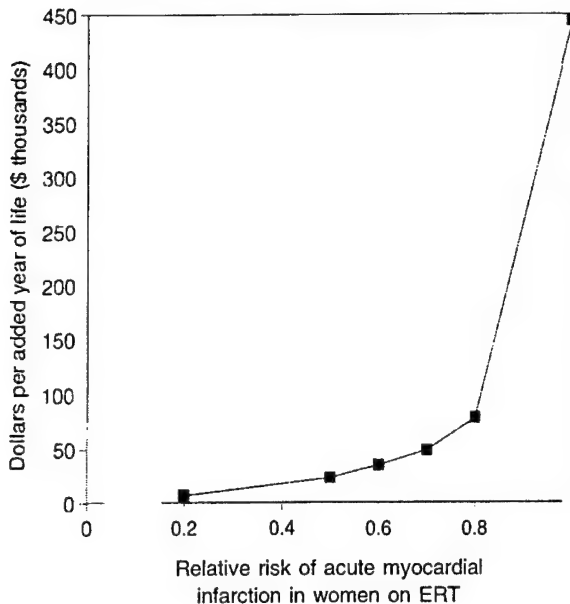
1. the relative risk of heart attack under ERT;
2. the relative risk of breast cancer after long-term ERT;
3. the relative risk of endometrial cancer under ERT; and
4. the degree to which ERT affects the rate of bone loss.

Analyses were conducted on the impact of changes in these assumptions on the cost-effectiveness ratios of two strategies: everyone on therapy for 20 years and everyone on therapy for 40 years.

### **Relative risk of heart attack**

Table 21 shows the cost-effectiveness ratios for two strategies (everyone on ERT for either 20 or 40 years) under the base case and the best and

**FIGURE 4: Impact of Coronary Heart Disease Benefits on the Cost Effectiveness of Lifetime ERT in 50-Year-Old Women**



SOURCE Office of Technology Assessment, 1995

worst case assumptions regarding the relative risk of heart attack while on ERT. Under the best case assumption, the relative risk of AMI is 0.20. Under the worst case assumption, it is 0.80.

As expected, assuming a smaller beneficial effect of HRT on heart attacks raises the cost per year of life gained from about \$23,000 to almost \$79,000 for a lifelong course of ERT. But if ERT follows the best case assumption, the cost per added year of life is reduced to slightly more than \$7,000, a very low cost-effectiveness ratio compared with that of other clinical preventive interventions.

Figure 4 shows the cost effectiveness of lifetime ERT in all women under a range of assumptions (0.2-1.0) regarding the relative risk of heart attack under ERT. The sensitivity of the cost-effectiveness ratio to changes in assumptions about HRT's effect on heart disease reflects the high incidence and lethality of heart disease and the high costs of treating it. If the suggestive evidence from

clinical trials on cardiac risk factors and from observational studies is correct, the cost per additional year of life from lifelong ERT lies within commonly used benchmarks for acceptability of clinical preventive services. Conversely, if the true heart disease benefit from ERT is small or nonexistent, the cost of ERT for each year of life gained is very high.

If heart disease benefits do not exist, limiting ERT to those with low bone mass would still be very costly for each year of life gained. For example, under the assumption of no heart disease benefits, placing on lifelong ERT only those whose measured BMD at age 50 lies more than 1 standard deviation below the mean results in a cost-per-added-year-of-life equal to \$157,041. This amount is substantially less than the cost-effectiveness ratio of placing all women on lifelong ERT (\$443,884), but it is still much higher than the ratio predicted for screening and selective ERT under the base case assumptions (\$27,486).

#### Relative risk of breast cancer

Table 22 shows the cost-effectiveness ratios for the best case and worst case assumptions regarding the relative risk of breast cancer after an extended duration of ERT. Under the best case assumption, HRT was assumed not to alter the relative risk of breast cancer, while under the worst case assumption, 10 or more years of HRT was assumed to increase the relative risk of breast cancer to 2.0.

Assuming the worst about the relative risk of breast cancer with HRT raises the cost per year of life gained for lifelong ERT for all women from \$23,000 to about \$44,000. Under the best case assumptions, the cost-effectiveness ratio is about \$16,000 per year of life gained.

#### Relative risk of endometrial cancer

Changing the assumptions about the relative risk of endometrial cancer does not alter cost-effectiveness ratios very much, (table 23) largely because the model assumes that endometrial cancer induced by ERT has an excellent prognosis and relatively low treatment cost.

**TABLE 22: Cost Per Added Year of Life for Two Osteoporosis Prevention Strategies<sup>\*</sup>**  
**Best- and Worst-Case Assumptions About Relative Risks of Breast Cancer**  
**Everyone on Therapy**  
**(95% confidence interval)**

	Number of years on ERT	
	20 years	40 years
Base case assumptions	\$45,761 (\$41,061-\$51,633) <sup>*</sup>	\$23,334 (\$21,744-\$25,151) <sup>*</sup>
Best case assumptions—breast cancer	\$37,734 (\$31,042-\$44,427)	\$16,105 (\$14,473-\$17,737)
Worst case assumptions—breast cancer	\$158,378 (\$105,494-\$316,054) <sup>*</sup>	\$43,765 (\$37,808-\$49,723)

<sup>\*</sup>All women are placed on therapy for either 20 or 40 years

<sup>\*</sup>Confidence Intervals computed based on Fieller's Theorem as cited in A.R. Willan and B.J. O'Brien, "Cost-Effectiveness Ratios in Clinical Trials From Deterministic to Stochastic Models," presented at the American Statistical Association meeting, Toronto, Canada, August 1994

SOURCE Office of Technology Assessment, 1995

**TABLE 23: Cost Per Added Year of Life for Two Osteoporosis Prevention Strategies<sup>\*</sup>**  
**Best- and Worst-Case Assumptions About Relative Risks of Endometrial Cancer**  
**Everyone on Therapy**  
**(95% confidence interval)**

	Number of years on ERT	
	20 years	40 years
Base case assumptions	\$45,761 (\$41,061-\$51,633) <sup>*</sup>	\$23,334 (\$21,744-\$25,151) <sup>*</sup>
Best case assumptions—endometrial cancer	\$42,496 (\$35,304-\$49,689)	\$21,039 (\$19,061-\$23,017)
Worst case assumptions—endometrial cancer	\$49,304 (\$39,694-\$58,914)	\$29,718 (\$25,810-\$33,625)

<sup>\*</sup>All women are placed on therapy for either 20 or 40 years

<sup>\*</sup>Confidence intervals computed based on Fieller's Theorem as cited in A.R. Willan and B.J. O'Brien, "Cost-Effectiveness Ratios in Clinical Trials From Deterministic to Stochastic Models," presented at the American Statistical Association meeting, Toronto, Canada, August 1994

SOURCE Office of Technology Assessment, 1995

### Relationship of HRT to bone loss

Table 24 shows how assuming that HRT reduces bone loss by 50 percent, rather than 100 percent as assumed in the base case, changes the cost-effectiveness ratios for the two ERT strategies. Under the lifetime ERT strategy, the assumption that ERT is only partially effective in maintaining

bone density hardly affects the estimated cost per year of life gained. Because all other assumptions are the same as those in the base case, the large gains in years of life resulting from lower risk of heart attack overwhelm other dimensions of effectiveness and maintain the cost-effectiveness ratio at a moderately low level.

**TABLE 24: Cost Per Added Year of Life for Two Osteoporosis Prevention Strategies<sup>a</sup>**  
**Worst-Case Assumptions About Effects of ERT on Bone Loss**  
**Everyone on Therapy**  
 (95% confidence interval)

	Number of years on ERT	
	20 years	40 years
Base case assumptions	\$45,761 (\$41,061-\$51,633) <sup>b</sup>	\$23,334 (\$21,744-\$25,151) <sup>b</sup>
Worst case assumptions—ERT and bone loss	\$62,342 (\$48,295-\$76,390)	\$27,994 (\$24,721-\$31,267)

<sup>a</sup>All women are placed on therapy for either 20 or 40 years

<sup>b</sup>Confidence intervals computed based on Fieller's Theorem as cited in A.R. Willan and B.J. O'Brien, "Cost-Effectiveness Ratios in Clinical Trials From Deterministic to Stochastic Models," presented at the American Statistical Association meeting, Toronto, Canada, August 1994

SOURCE: Office of Technology Assessment, 1995

**TABLE 25: Cost Per Added Year of Life for Two Osteoporosis Prevention Strategies<sup>a</sup>**  
**Best- and Worst-Case Assumptions About Four Uncertain Parameters**  
**Everyone on Therapy**  
 (95% confidence interval)

	Number of years on ERT	
	20 years	40 years
Base case assumptions	\$45,761 (\$41,061-\$51,633) <sup>b</sup>	\$23,334 (\$21,744-\$25,151) <sup>b</sup>
Best case assumptions—four uncertain parameters	\$17,427 (\$15,915-\$18,939)	\$1,559 (\$1,467-\$1,650)
Worst case assumptions—four uncertain parameters	neg. effect., pos. costs	\$1,465,434 (\$436,834-undefined) <sup>b</sup>

<sup>a</sup>All women are placed on therapy for either 20 or 40 years

<sup>b</sup>Confidence intervals computed based on Fieller's Theorem as cited in A.R. Willan and B.J. O'Brien, "Cost-Effectiveness Ratios in Clinical Trials From Deterministic to Stochastic Models," presented at the American Statistical Association meeting, Toronto, Canada, August 1994

SOURCE: Office of Technology Assessment, 1995

#### Simultaneous changes in four uncertain parameters

OTA analyzed how the cost-effectiveness ratios change if all four of the parameters are held simultaneously to their worst case values or to their best case values. Table 25 presents the results for the two preventive strategies. The range of cost-effectiveness values widens dramatically to span a very low ratio (\$1,559 per year of life gained for 40 years of therapy) and a prohibitively high ratio (\$1.5 million per year of life gained for 40 years

HRT). Because the estimated mean years of life gained are very small under the worst case scenario, the approximate 95-percent confidence interval for the estimate is very wide. Again, when the effects of an intervention are close to zero, one can have little confidence in the mean reported cost-effectiveness ratio.

The best case/worst case analysis gives an extremely wide envelope of potential cost-effectiveness ratios for ERT. Because our base case

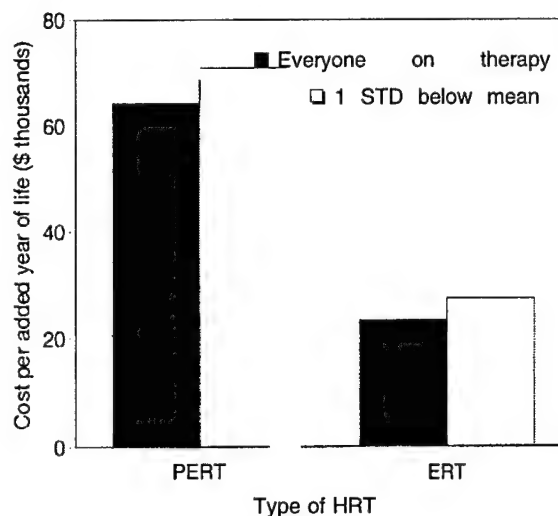
assumptions predicted cost-effectiveness ratios for lifelong ERT strategies that were reasonably low (i.e., reasonably cost effective) compared with other accepted clinical preventive services, any uncertainty favoring the best case merely reinforces the cost effectiveness of lifelong ERT. The very high cost-effectiveness ratio in the worst case scenario, however, means that we cannot rule out the possibility that any ERT strategy (with or without BMD screening) would be a very poor investment for society.

### Outcomes with PERT

PERT reduces the excess risk of endometrial cancer in women on HRT, but it may also reduce HRT's heart disease benefits. OTA analyzed the cost effectiveness of a lifelong regimen of PERT assuming that 1) the risk of endometrial cancer with PERT, is not elevated over population levels and 2) the relative risk of heart attack in women on PERT compared with those not on therapy is 0.8. All other assumptions followed the base case. (See table 2 above.) Figure 5 compares the resulting cost-effectiveness ratios of two preventive strategies with those of the same strategy using ERT.

The PERT strategies are less cost effective because assumptions about heart disease have a big impact on the analysis.<sup>37</sup> Although PERT reduces incidence and lowers treatment costs of endometrial cancer, it also lowers heart disease benefits, which far outweigh the consequences of endometrial cancer. Of course, if ERT itself has no heart disease benefits, the addition of progestins to the HRT regimen improves the cost-effectiveness ratio, but the cost-effectiveness ratios of either regimen would be very high. (For a 40-year course of HRT in all women, the cost per added year of life

FIGURE 5: Cost Effectiveness of PERT v. ERT



SOURCE: Office of Technology Assessment 1995

assuming no heart disease benefits is \$443,884 for ERT and \$262,673 for PERT.)

### Initiating Osteoporosis Screening/HRT at Age 65

Is osteoporosis prevention at menopause better or worse than initiating prevention at a later age, when the risk of hip fracture and heart disease have increased? Beginning HRT in elderly women has been proposed as a way to reduce the total duration of exposure to HRT in these women, thus reducing the risks of breast and endometrial cancer, while having HRT present during the ages of highest risk of heart disease and hip fracture.

Modeling the impact of BMD screening and/or HRT on bone loss, heart disease, breast cancer, endometrial cancer, and gallbladder disease is even more uncertain for a population of 65-year-old

<sup>37</sup>If the relative risk of CHD were the same for both ERT and PERT then the cost-effectiveness ratios would be similar. For example, if the relative risk of CHD is 0.8 for both ERT and PERT, the cost per added year of life of a lifetime course of ERT for all women is \$78,860 and the cost per added year of life for the same strategy using PERT is \$64,376.

women than it is for a population of 50-year-old women, because there is much less information available on effectiveness and risks of HRT in women who begin therapy at 65 years of age.<sup>38</sup>

OTA analyzed the cost effectiveness of initiating a screening program in women at age 65 under the base case assumptions regarding the effect of ERT on disease. Specifically, OTA assumed that:

1. ERT will stop further bone loss while a woman is on therapy;
2. the relative risk of heart attack is 0.5 while on therapy;
3. the relative risk of breast cancer is 1.35 after 10 years of therapy;
4. the relative risk of endometrial cancer is 3.5 as soon as therapy begins and 7.0 after 10 years for the duration of therapy; and
5. the relative risk of gallbladder disease is 2.5 while on therapy.

Table 26 shows the results of the analysis for strategies in which women are screened at age 65 and placed on ERT for 20 years. Regardless of the BMD threshold for ERT, prevention is cost saving. That is, it not only lengthens life on average but also reduces health care costs. Putting all women on therapy both provides the greatest cost saving and adds the greatest number of years of life to the cohort.

Much of the medical benefit and reduced cost predicted by the model stems from assumed reductions in the risk of heart attacks for women on ERT. Since there is no evidence that women first placed on ERT at age 65 do indeed have a reduced heart attack risk, OTA examined the sensitivity of the results of assuming the relative risk of heart attack is 1.0.

Placing on ERT for 20 years only those women whose BMDs are below the mean costs almost \$184 million per 100,000 women screened and adds about 2,000 years of life to the cohort.<sup>39</sup> The mean cost per discounted year of life gained is \$90,117 (approximate confidence interval is \$45,191 to \$135,033). Thus, if there are no cardiac benefits to HRT when it is begun at 65 years of age, an osteoporosis screening and HRT program that begins at age 65 will deliver health benefits at a cost that lies above commonly accepted benchmarks for preventive interventions. The risks and benefits of initiating HRT at older ages need more study.

### ■ Cost Effectiveness of A Hypothetical Targeted Osteoporosis Drug

HRT is at present the only therapy approved for marketing to prevent the reduction in bone mass that accelerates in women around menopause and eventually contributes to fractures. Other classes of drugs are currently under investigation as targeted approaches to maintaining or increasing bone mass in women with osteoporosis (19, 54, 61, 98, 110). One drug approved today for the treatment of women with established osteoporosis is injectable calcitonin, although questions remain about calcitonin's long-term efficacy on bone and fracture. Calcitonin is approved for treatment of osteoporosis, but it has not been approved for prevention of osteoporosis (29, 70).

The bisphosphonate class of drugs has received considerable development effort. The most well-studied bisphosphonate, etidronate, was recommended for rejection by an FDA medical advisory panel in November 1994. Researchers today are focusing on the bisphosphonate alendronate,

<sup>38</sup> Although studies of HRT's impact on heart disease, osteoporosis, and other disease have included elderly women, few of these women began HRT in old age. The benefits of HRT initiated many years after menopause may differ from the benefits in those who have been on HRT for many years. For example, the benefit of HRT on heart disease may be lower in women who already have substantial atherosclerosis. The ability of HRT to reduce hip fracture risk may be limited in women with already compromised bone structure.

<sup>39</sup> Both costs and effectiveness are discounted to their present value in the screening year at an annual rate of 5 percent.

## 44 I Effectiveness and Costs of Osteoporosis Screening and Hormone Replacement Therapy

**TABLE 26: Cost Effectiveness of Screening/HRT Beginning at 65 Years of Age\***  
per 100,000 women screened  
(\$ millions)

	Baseline: no therapy	BMD threshold for therapy		Everyone on therapy
		1 STD below mean	Below mean	
Number who complete therapy "	0	13,540	42,828	85,564
Fatal heart attacks	8,929	8,380	7,458	5,972
Number of breast cancer cases	7,292	7,549	7,965	8,677
Number of endometrial cancer cases	1,679	2,625	4,488	7,297
Number of hip fractures	17,190	15,918	14,102	11,781
Number of gallbladder removals	8,929	10,633	14,239	19,581
Cost of treating breast cancer (undiscounted)	\$313	\$322	\$336	\$361
Cost of treating breast cancer (discounted)	\$216	\$221	\$227	\$240
Cost of treating endometrial cancer (undiscounted)	\$29	\$32	\$37	\$45
Cost of treating endometrial cancer (discounted)	\$20	\$22	\$25	\$29
Cost of heart attacks (undiscounted)	\$1,852	\$1,738	\$1,547	\$1,239
Cost of heart attacks (discounted)	\$983	\$915	\$797	\$609
Cost of treating hip fractures (undiscounted)	\$394	\$365	\$323	\$270
Cost of treating hip fractures (discounted)	\$201	\$187	\$168	\$144
Cost of treating gallbladder disease (undiscounted)	\$100	\$119	\$159	\$219
Cost of treating gallbladder disease (discounted)	\$67	\$81	\$110	\$153
Cost of hormone replacement therapy (undiscounted)	\$0	\$64	\$202	\$405
Cost of hormone replacement therapy (discounted)	\$0	\$44	\$141	\$281
Cost of BMD screening (undiscounted)	\$0	\$10	\$10	\$0
Cost of BMD screening (discounted)	\$0	\$10	\$10	\$0
Total lifetime costs (undiscounted)	\$2,688	\$2,650	\$2,615	\$2,538
Total lifetime costs (discounted)	\$1,487	\$1,480	\$1,478	\$1,456
Years of life lived per 100,000 (undiscounted)	1,773,287	1,779,926	1,791,992	1,811,804
Years of life lived per 100,000 (discounted)	1,155,306	1,158,286	1,163,942	1,173,341
Dollars saved		\$7	\$8	\$31
Years of life gained		2,981	8,637	18,035

\*20 years of therapy.

KEY: BMD = bone mineral density; HRT = hormone replacement therapy, STD = standard deviation

NOTE: Discount rate = 5% for both years of life and costs Costs discounted to present value at age 65 years Base case assumptions

SOURCE: Office of Technology Assessment, 1995



which has been shown to be effective in preventing bone loss (10, 143).

What would OTA's cost-effectiveness model predict about a hypothetical drug targeted to bone-mass maintenance without the side-effects attributed to HRT? We analyzed two osteoporosis prevention strategies for 50-year-old women: screening for BMD and placing all women whose BMD lies below the mean on preventive doses of the drug; and placing all women (regardless of BMD) on the drug. We assumed the following about the intervention: 1) it would preserve bone mass for the duration of therapy; 2) it would involve *no* increased risks of cancer, gallbladder disease, or any other unintended side effects; and 3) it would have no beneficial effect on heart disease.<sup>40</sup>

The analysis was based on two alternative assumptions about the annual cost of such a medication: 1) that it would cost the same as PERT; and 2) that it would cost \$1,000 per year. The latter assumption is probably more realistic about a new drug for the prevention of a chronic illness with major morbidity.<sup>41</sup>

Table 27 describes the results of the analysis. Regardless of the annual cost of the drug or whether BMD screening is used to target the drug to those at highest risk of osteoporosis, the lifetime cost per added year of life is well above \$100,000. If the drug is introduced at a total annual cost of \$1,000, the lifetime cost would be very high relative to the gains in years of life, particularly if all women are placed on therapy.

Were a new drug to be approved that meets the assumptions laid out above, the case for limiting therapy to those at highest risk for osteoporosis

would be strong. Even then, a strategy of BMD screening and selective therapy would be difficult to justify on cost-effectiveness grounds without better information about dimensions of effectiveness that have not been included in the present model—the quality-of-life impacts associated with osteoporosis-related fractures. OTA's model included only length-of-life and cost impacts of hip fractures. Whether the decrements in the quality of life associated with hip fractures and other fractures would bring a quality-adjusted cost-effectiveness ratio into line with customary benchmarks is a research issue that may be worth careful exploration in anticipation of the development of a targeted osteoporosis drug sometime in the future.

### ■ Low Compliance with HRT: Implications for Cost Effectiveness

OTA's analysis assumed that women who enter a screening or HRT program would stick with the therapy for its entire course. Although the proportion of post-menopausal U.S. women who use HRT has increased in the past two decades (21), until recently the duration of use and the average dose actually declined (116). This is due in part to the growing evidence that risk of cancer may be related to the dose and duration of HRT. Even when women are prescribed HRT, a substantial proportion (20 to 60 percent) never have their prescriptions filled (125). The five-year full compliance rate for women who begin post-menopausal HRT is between 5 and 34 percent (125).<sup>42</sup>

Recently introduced HRT regimens, such as continuous-combined HRT or estrogen patches, may increase compliance in the future, and better

<sup>40</sup> Calcitonin and the bisphosphonates appear to have no major effects other than on bone.

<sup>41</sup> Commonly prescribed preventive medications for cholesterol reduction cost on the order of \$750 to \$2,000 per year (45). In 1994, the average wholesale price of a yearly dose of injectable calcitonin for treatment of osteoporosis was \$3,545.98 (1).

<sup>42</sup> Low compliance with HRT has many reasons. In general, compliance with a drug regimen is lower when patients suffer no physical symptoms, patients are not convinced the medication will help, patients are afraid of side effects, or symptoms disappear before the end of treatment (138). Many women may be resistant to taking HRT because it is *not natural* (91). They also discontinue HRT because of side effects they find unacceptable, such as resumed menstruation, breast tenderness, weight gain, headaches, and abdominal bloating (93).

**TABLE 27: Cost Effectiveness of a Lifetime Course of a Hypothetical Osteoporosis Preventive Therapy in Women Beginning at 50 Years of Age<sup>a</sup>**  
**per 100,000 women**  
**(\$ millions)**

	Baseline: no therapy	1 STD below mean	Everyone on therapy
<b>For therapy = \$258/year</b>			
Number who complete therapy	0	13,897	87,727
Fatal heart attacks	8,570	8,619	8,675
Number of breast cancer cases	10,135	10,220	10,199
Number of endometrial cancer cases	2,378	2,398	2,379
Number of hip fractures	16,985	14,633	6,588
Number of gallbladder removals	12,576	12,596	12,678
Years of life lived per 100,000 (undiscounted)	3,018,098	3,020,287	3,028,149
Years of life lived per 100,000 (discounted)	1,549,499	1,549,958	1,551,618
Total lifetime costs (undiscounted)	\$2,862	\$2,975	\$3,389
Total lifetime costs (discounted)	\$997	\$1,067	\$1,327
Extra costs incurred		\$70	\$330
Gain in years of life lived		459	2,119
Cost effectiveness ratio (dollars per year of life added)		\$152,288	\$155,816
<b>For therapy = \$1000/year</b>			
Total lifetime costs (undiscounted)		\$3,279	\$5,523
Total lifetime costs (discounted)		\$1,234	\$2,412
Extra costs incurred (undiscounted)		\$237	\$1,445
Gain in years of life lived		650	1,932
Cost effectiveness ratio (dollars per year of life added)		\$363,752	\$747,894

<sup>a</sup>Therapy is assumed to stop bone loss at the age of initiation with no other health effects

NOTE Discount rate = 5% for both years of life and costs. Costs discounted to present value at age 50 years

SOURCE Office of Technology Assessment, 1995

information about risks and benefits of therapy may help as well (93), but it is unrealistic to assume that most women who begin HRT will remain on it for the rest of their life.

What does low long-term compliance with therapy mean for the cost effectiveness of HRT? The data in table 20 show clearly that HRT is substantially less cost effective with lower rates of compliance. If 50 percent of women were to terminate therapy after only 10 years while the rest of the population remains on therapy for 40 years, for example, the cost effectiveness of ERT in the population as a whole would rise to about \$73,000. Thus, unless present compliance rates can be sub-

stantially increased, an HRT strategy is not likely to be very cost-effective.

Because low bone density does not have obvious symptoms unless fracture occurs, bone-density measurement may increase commencement and maintenance compliance with HRT. Physicians could use densitometry to help patients who are undecided about initiating HRT to *visualize* their low bone density (96). In addition, maintenance compliance might be improved by the use of densitometry in following patients' bone density over time.

Recent evidence suggests that women who have had below-average bone density confirmed by densitometry may be more likely to commence HRT as a preventive measure for osteoporosis (118). In a study of a random sample of women who had undergone densitometry, 38 percent of those who were told their BMD was below normal began taking HRT, compared with 8 percent of those who were told their BMD was normal or high.<sup>43</sup>

Given the very real barriers to compliance with HRT that exist in the general population and the evidence that BMD screening may increase compliance among those at highest risk of osteoporosis, a strategy of BMD screening coupled with HRT *only* in those at highest risk of fracture may be more cost-effective in practice than a strategy that encourages all women to commence HRT. The cost per added year of life may still be very high if the compliance obtained from such a strategy is incomplete.<sup>44</sup> Thus, even if screening and selective HRT can substantially increase long-term rates of compliance, the cost of prevention may still be high compared with its medical benefits. Furthermore, the use of BMD screening as a tool to increase compliance must be evaluated against other methods of improving long-term compliance.

### COMPARISON OF OTA'S RESULTS WITH OTHER COST-EFFECTIVENESS ANALYSES

Several earlier studies examined the health and cost impacts of long-term HRT, with or without BMD screening. None of these studies included the same components of effect, and each made dif-

ferent assumptions about the benefits, risks, and costs of screening and HRT.

Weinstein analyzed the cost effectiveness of placing women on estrogen therapy for 15 years beginning at age 50 (141, 142). Unlike OTA, Weinstein attributed no beneficial cardiovascular effects to HRT. On the other hand, he assumed that HRT would reduce the frequency of wrist fractures (and therefore the cost of treating them) as well as those of hip fractures. Weinstein's assumptions about patterns of risk of hip fracture, endometrial cancer, and breast cancer in women placed on HRT also differed from those of OTA. Finally, Weinstein assigned subjective *quality-of-life* weights to years of life lived in the presence of the diseases and conditions affected by HRT. These quality-of-life weights were based on the authors' best judgment about the value of one year of life lived with hip fracture compared with a year of life lived in perfect health.

The estimated cost per quality-adjusted year of life gained under a 15-year-long regimen of HRT in all women was \$24,000 (in 1980 dollars). This is somewhat lower than OTA's estimate for a 15-year course of therapy, whose estimated average cost lies between \$46,000 (20 years' therapy) and \$127,000 (10 years' therapy).

Tosteson and colleagues examined the cost effectiveness of estrogen/progestin therapy and BMD screening using more recent data on hip fracture risks than was available to Weinstein (127). Some of the assumptions in that analysis more closely approximate those of OTA. For example, they assumed that HRT would stop bone loss for the duration of therapy. Because the HRT tested in their analysis included progestin, Toste-

<sup>43</sup> This study is difficult to interpret, because it did not control for differences in the level of BMD. The study investigators did not state how many women were already planning to begin HRT before BMD screening. How much higher compliance would be in low-BMD women who are given bone-density information than in low-BMD women who are not told their BMD levels remains an open question. There is also no information about what physicians recommended to their patients, or whether HRT was prescribed. Studies of compliance with HRT have shown that it is strongly affected by what people are told by their physicians and what women believe about HRT's risk and benefits.

<sup>44</sup> For example, under a strategy of screening and ERT for women whose BMD is in the lowest 16 percent of the population, if 50 percent of the high-risk women stop ERT after 10 years of therapy, the average cost would be \$90 thousand per added year of life, compared with \$27 thousand if all high-risk women stayed on therapy for the rest of their life. (See table 20).

son and colleagues assumed neither beneficial heart disease effects nor increased risks of endometrial or breast cancer in women on HRT. Thus, the Tosteson analysis rests primarily on the beneficial effects of HRT on osteoporotic fractures.

Tosteson presented results both in terms of cost per added year of life and cost per year of life, adjusted for the quality of life in various health states. The quality adjustment weights were based on subjective estimates developed by Hillner and colleagues based on the judgement of a small group of experts (55).<sup>45</sup> OTA did not apply quality-of-life weights, but how such weighting would affect OTA's results is unclear, since the deleterious effects on the quality of life with breast or endometrial cancer, or of HRT itself, are accompanied by improvements in the quality of life when hip fractures and heart disease are avoided. Tosteson did not address the negative effects of HRT on breast cancer, endometrial cancer and gallbladder disease; hence, their quality adjustments decreased the cost-effectiveness ratio.

Tosteson found that the cost per additional year of life lived (before adjusting for quality of life) was \$86,100 (in 1990 dollars) for a 15-year course of HRT. This compares with OTA's estimate in the range of \$46,000 (20 years' therapy) to \$127,000 (10 years' therapy).

Screening women for BMD and placing on HRT only those at high risk of fracture was more cost effective than treating all women with estrogen-progestin therapy. For example, placing on HRT only those women whose BMD values were below 0.9 gm/cm<sup>2</sup> resulted in a cost per year of life gained of \$14,620 (in 1990 dollars). The relatively low costs of selective HRT (compared with those

of universal HRT) are to be expected in a model that predicts no heart disease benefits.

A recent Australian study provides estimates of the cost per QALY of various HRT strategies initiated at menopause (23). The authors adopted the subjective quality weights developed by Weinstein (142). In contrast to Weinstein, they included heart disease benefits, valuing each year of life following a heart attack at the same value as a year of life following hip fracture. They also assumed that HRT would have no impact on breast cancer incidence. The study did not include the costs of nursing home stays following hip fracture and made assumptions about the risks and costs of endometrial cancer that differed from those of OTA. These authors concluded that a 15-year course of HRT would cost approximately \$46,000 (1988 Australian dollars) per QALY with ERT and \$40,000 per QALY with PERT if the relative risk of heart attack is 0.5 with ERT and 0.75 with PERT.

Other analysts have also estimated the cost impacts of osteoporosis screening and treatment, but their work is less directly comparable with OTA's study. Ross and colleagues evaluated the potential annual costs and savings associated with screening all women at age 50 and a lifetime course of HRT (116). They assumed that HRT would reduce bone loss by 50 percent throughout the period and predicted the impact of HRT on the incidence of fractures using data from a sample of 2,000 women. Placing all women on HRT for their lifetimes would reduce lifetime fracture frequency by 43 percent (compared with a reduction of 53 percent predicted under OTA's base case assumptions).

<sup>45</sup> For example, one year spent in a nursing home following a hip fracture was assumed to be worth 0.36 years of life without disease.

Ross and Wasnich estimated the national cost of osteoporotic fractures in women at \$5.69 billion (in 1987 dollars).<sup>46</sup> They assumed that BMD screening would cost \$60 (compared with OTA's estimate of \$100) and that annual HRT would cost \$75 (compared with OTA's estimate of \$269). Assuming a proportional reduction in national fracture costs with reductions in fracture incidence, Ross and Wasnich predicted that placing all women on HRT would save \$2.43 billion per year (1987 dollars) in fracture costs, which would just pay for the costs of HRT. Screening for bone mineral content and placing only those women with the lowest 50 percent on HRT would reduce the national costs of osteoporotic fractures by \$1.88 billion per year which, when combined with the costs of screening and selective HRT, would lead to a net savings of \$760 million per year.

The finding that the national cost of illness actually declines with HRT, even when cardiac benefits are not considered, is due to several aspects of the approach taken by Ross and his colleagues. First, the costs of screening and therapy assumed in that study are substantially lower than those assumed by OTA and other investigators. Second, the national cost of osteoporotic fractures includes cost items that are excluded from OTA's analysis.<sup>47</sup> Third, Ross and Wasnich did not include the costs of treating other diseases induced

by HRT, such as gallbladder disease, endometrial cancer, and breast cancer.

It is also worth noting that the conclusion that BMD screening and selective HRT in those at high risk will actually increase savings associated with osteoporosis prevention compared with universal HRT is based on the exclusion of heart disease benefits from the model. In OTA's analysis, heart disease benefits are in large part responsible for the greater cost effectiveness of a lifelong regimen of HRT for all women.

Clark and Schuttinga recently analyzed the present value of net direct and indirect health care costs of screening for BMD at 50 years of age and placing high and moderate-risk women on a 15-year estrogen/progestin strategy (27). They assumed that a 15-year course of HRT would reduce fracture risk by 50 percent after the first five years and through the rest of the woman's lifetime. They estimated the average cost of hip fracture at \$41,723 (compared with approximately \$23,000 assumed by OTA).<sup>48</sup>

Slightly less than 10 percent of total hip fracture costs estimated by Clark and Schuttinga are lost earnings. Clark and Schuttinga included the net costs of vertebral fractures (assumed to result in hospitalization in 50 percent of cases) and of all other fractures.<sup>49</sup> Assuming that 1) 90 percent of

<sup>46</sup> This estimate was taken from a 1984 study of the costs of musculoskeletal conditions conducted by the American Academy of Orthopedic Surgeons (3). The authors of that study estimated the annual national costs associated with osteoporosis at \$6.14 billion in 1984 dollars. Ross and colleagues updated the cost estimate to 1987 dollars and multiplied the result by 80 percent to account for the proportion of osteoporotic fractures assumed to occur in women (80%).

Because it is difficult to identify the true contribution of osteoporosis to fracture incidence, the authors of the 1984 study had to estimate the proportion of fractures attributable to osteoporosis. The 1984 report does not specify these assumptions, but in the report 32 percent of total fracture-related inpatient hospital costs across all ages was attributed to osteoporosis and more than 50 percent of all nursing home cost associated with fractures was attributed to osteoporosis.

<sup>47</sup> The 1984 estimate of osteoporosis costs includes several items that are excluded from OTA's estimate of the costs of osteoporotic fractures. First, the study includes the costs of all fractures, whereas OTA's analysis is limited to hip fractures (3). Even within hip fractures, however, about 16 percent of the 1984 estimate is for cost items excluded by OTA. In particular, 7 percent was attributed to nonhealth sector goods and service (e.g., the value of unpaid family care); 2 percent was attributed to administration of the system; and 7 percent was attributed to indirect costs (i.e., lost earnings). OTA excluded these cost items either because data were not accurate or the cost item is inappropriate for a cost-effectiveness analysis. See OTA's background paper on hip fractures for a detailed discussion (132).

<sup>48</sup> Clark's higher hip fracture costs are due principally to two factors: 1) a higher estimate of hospital costs (\$11,600 vs. \$7,623 for OTA); and 2) the use of an estimate for nursing home costs implies that all hip fracture patients spend a full year in a nursing home.

<sup>49</sup> The source of data on the incidence of different kinds of fractures is not given in the paper by Clark and Schuttinga.

the high risk group and 70 percent of the mid-risk group would comply with HRT therapy; 2) BMD measurement would cost \$150 (compared with \$100 in OTA's model); and 3) HRT would cost \$190 per year (compared with \$269 in OTA's model), Clark and Schuttinga concluded that the program would save \$5.1 million in net national costs per 100,000 women screened.

The optimistic forecast of net national cost savings for BMD screening and HRT in this analysis, compared with that of both OTA and Tosteson and Weinstein, is explained in large part by the relatively low annual HRT costs and the assumption that HRT would reduce fracture risk by 50 percent throughout the rest of a woman's life despite the discontinuation of therapy (compared with OTA's estimate of a lifetime decrease of roughly 35 percent for HRT of similar duration). Inclusion of indirect costs (lost earnings) and the costs of vertebral and other fractures in the national cost of osteoporosis also raises the potential cost savings associated with HRT. And the assumption that 50 percent of vertebral fractures would result in hospitalization, an assumption that is not supported by data, clearly increases the cost savings attributable to HRT.

On the other hand, Clark and Schuttinga assumed higher BMD screening costs than those of OTA. They also assumed lower compliance with therapy, which depresses net cost savings, and they assumed a higher discount rate (6 percent versus 5 percent used by both OTA and Tosteson and Weinstein.) These differences have a relatively small impact on the resulting estimates of cost savings compared with the differences in impacts on fracture rates and HRT cost assumptions.

As with all other analyses that assumed no heart disease benefits, Clark and Schuttinga's study found that BMD screening and selective placement on HRT of those at highest risk of fracture saves more money than placing all women on HRT.

## SCREENING RECOMMENDATIONS OF EXPERT GROUPS

A number of technology assessment agencies of other governments have recommended against bone-density measurement as a routine procedure for screening of osteoporosis in all postmenopausal women, including France (2); Germany (47); Britain (128, 130, 139); Spain (60, 99, 119); Australia (9); Finland (44); and Canada (48). The World Health Organization (WHO) also recommended against general screening of postmenopausal women for osteoporosis (147). Some of these groups did recommend BMD measurements in menopausal women with multiple risk factors (2, 9, 137, 147). Other government agencies are planning an assessment, including the Netherlands (89) and Sweden (126).

In the United States, the U.S. Preventive Services Task Force (137) and the National Center for Health Services Research (135, 136) have not recommended general screening of bone density in menopausal women. Both the OHTA and USPSTF have new assessments near completion. The new USPSTF recommendations, due out this year, are not likely to change regarding bone density screening (64).

Several medical organizations in the United States have also issued recommendations regarding BMD screening. The American College of Obstetrics and Gynecology does not recommend routine BMD screening for all postmenopausal women, but densitometry has a place in screening women who are at increased risk for osteoporosis (4). They also mention that BMD screening may improve compliance with HRT.

The American College of Physicians does not recommend screening of all postmenopausal women for osteoporosis, but recognizes a role for BMD measurements in women who are undecided about HRT (5). The American College of Rheumatology recommends BMD measurements in women who have risk factors for osteoporosis:



a family history of osteoporosis, early onset of menopause, and low body weight. They also recommend BMD screening in women with other medical conditions that predispose to osteoporosis, such as primary hyperparathyroidism and long-term glucocorticoid therapy (6).

A consensus conference sponsored by the European Foundation for Osteoporosis and Bone Disease, the National Osteoporosis Foundation, and the National Institute of Arthritis and Musculoskeletal Diseases concluded that bone-mass measurement is the best approach to screen individuals for their risk of developing osteoporosis (41).

## CONCLUSIONS AND POLICY IMPLICATIONS

OTA's analysis of the costs and effectiveness of osteoporosis screening and HRT, under base case assumptions, suggests that it would be reasonably cost effective to offer ERT at age 50 (the time of menopause) to all women who commit to a lifelong course of ERT. Entering all eligible women on lifelong ERT would cost roughly \$257 million per 100,000 women entered in the program and provide about 11,000 extra years of life (discounted to their present value) to the program enrollees. The net cost per added year of life is \$21,600 to \$25,000 (in 1993 dollars). These estimated costs per added year of life are comparable to other preventive interventions currently paid for by public and private third-party payers. Biannual screening mammograms, for example, were legislated as a covered Medicare benefit based in part on evidence that showed a cost of \$34,000 per added year of life (in 1987 dollars) (131).

Screening women for low BMD and targeting those at highest risk of osteoporosis for ERT is also reasonably cost effective. Entering eligible women with BMD values one standard deviation below the mean on lifelong ERT would cost roughly \$50.5 million per 100,000 women entered in the program and provide 1,800 extra years of life (discounted to their net present value) to the program enrollees. The net cost per added year of

life is \$18,900 to \$47,800 (in 1993 dollars). Though aggregate program costs decline with fewer people on therapy, aggregate benefits also decline, and the net cost per added year of life does not change much. Screening may help to identify those women who would stand to gain the most in life extension benefits from HRT, but other methods of selecting women who would gain the most from HRT, such as identifying those at highest risk of heart disease or at lowest risk of breast cancer, might be less costly and more effective than BMD screening.

Shorter durations of HRT use—10 to 20 years—are much less cost-effective than are longer treatment durations, largely because substantial medical benefits accrue only when women stay on the therapy into old age, when the frequency of hip fractures and heart disease rise dramatically. OTA's model suggests that taking HRT for only 10 years after menopause is extremely costly, regardless of whether BMD screening is used to target therapy.

OTA's conclusions about the costs and effectiveness of osteoporosis screening and HRT are tempered by substantial uncertainty about the benefits and risks of HRT. The impacts of HRT on breast cancer, hip fracture, heart disease, gallbladder disease, and endometrial cancer have not been estimated in adequate randomized controlled clinical trials. Because almost all studies of HRT's impacts on these diseases are observational, one cannot exclude the possibility that selection bias affects their results. The most important factor affecting the tentativeness of OTA's conclusions is the uncertainty about HRT's impact on heart disease, because the estimated cost effectiveness of screening and HRT is especially sensitive to assumptions about heart disease risk.

OTA's estimated cost-effectiveness ratios assume the existence of substantial reductions in heart disease incidence in women on HRT. Without such benefits, the net life-extending effects of HRT are substantially reduced, and the cost of achieving such benefits may be extremely high. Unfortunately, the evidence of heart disease benefits is based principally on observational studies

which, though they are largely consistent in showing a protective effect of HRT, could be substantially confounded by selection bias.

If HRT proves to have little or no heart disease benefit, screening women for BMD and limiting HRT to those with low BMD values would be more cost-effective than giving HRT to all women, but the costs of screening and HRT would still be extremely high relative to the life-extension benefits received. If HRT has little or no heart disease benefit, BMD screening might meet commonly accepted cost-effectiveness benchmarks for clinical preventive services only if it were shown that the improvements in quality of life from prevention of hip fracture substantially outweighed the loss of quality of life from HRT-induced breast cancer.

Estimates of the cost effectiveness of osteoporosis screening and HRT are very sensitive to assumptions about women's compliance with HRT. Realistic expectations about compliance with HRT, especially over a lifetime of treatment, reduce the cost effectiveness that can be expected of the osteoporosis prevention strategies examined in this paper. If compliance remains as low as it has been, all of the screening/HRT strategies would be very costly for the benefits they convey. Long-term compliance with HRT might improve if physicians became more aggressive in recommending the therapy. Newer HRT regimens currently under development may reduce the incidence of bleeding and other adverse effects that tend to discourage long-term compliance with HRT. Nevertheless, policymakers must consider whether encouraging women to embark on a life-long HRT regimen through education programs or payment for preventive HRT is likely to be effective in delivering the benefits that such a regimen promises.

Some experts have suggested that BMD screening has a role in the assessment of menopausal women who would accept HRT if it were shown that they were at high risk of osteoporosis (5). Experts have suggested that BMD screening may also be useful in improving women's long-term compliance with HRT (118), because a

woman's awareness that her bone density is low may encourage that woman to remain on HRT. But the results of BMD screening could also discourage those with high measured bone densities from remaining on HRT. The costs and long-term effectiveness of using BMD screening for increasing uptake and compliance with HRT needs to be evaluated. The use of BMD screening for these purposes needs to be judged against other methods of increasing HRT uptake and compliance.

OTA's analysis suggests that it would be even more cost-effective to offer ERT to women at age 65 than at age 50. This conclusion, however, depends on extrapolating the heart disease benefits seen in women who begin ERT at menopause to women who begin therapy at older ages. Conclusions about the costs and effectiveness of initiating HRT in the elderly are even more tentative because there is far less information about the effects of HRT initiated at age 65 than there is about HRT initiated at age 50. If, in fact, HRT has substantially less effect on heart disease when initiated at age 65 than when initiated at age 50, beginning HRT at older ages would be less cost-effective than beginning it at age 50.

The OTA cost-effectiveness analysis is intended to guide overall public health policy, including decisions about educational programs or payment for screening or HRT. This analysis is not intended to guide individual decisions regarding BMD screening or long-term HRT. Individual women's risks of the various conditions and diseases affected by HRT vary, as do their assessments of the quality-of-life implications of various outcomes. For example, some women may wish to avoid increasing their risk of cancer regardless of the achievable heart disease benefits or hip fracture risk reduction.

To summarize, if OTA's best estimates of the impacts of screening and HRT on health outcomes and costs are accurate, a life-long course of ERT for all women beginning at menopause is a good investment for society compared with other accepted preventive services. The uncertainty surrounding critical parameters, however, means that we cannot be absolutely assured that HRT is rela-



tively cost-effective. And barriers to compliance with long-term therapy cast doubt on whether the potential benefits, even if they are accurately forecast, will be achieved in practice.

The only condition under which BMD screening would become more cost-effective than giving HRT to everyone would be if it were shown, first, that there are no heart disease benefits from HRT and, second, that hip fractures and other osteoporotic fractures had a dramatic effect on quality of life. There are no data on quality-adjusted life years in persons with hip fracture or other osteoporotic fractures.

## REFERENCES

1. 1994 Physicians GenRx. The Complete Drug Reference (Smithtown, NY: Data Pharmaceutica Inc., 1994).
2. Agence Nationale pour le Développement de l'Evaluation Médicale, *Evaluation of Bone Mineral Density Measurement* (Paris, France: ANDEM, October 1991).
3. American Academy of Orthopaedic Surgeons, *Cost-Effectiveness of Hormone Replacement Therapy in the Menopause*, K.L. Grazier, T.L. Holbrook, J.L. Kelsey, et al., (eds.) (Chicago, IL: 1984).
4. American College of Obstetricians and Gynecologists, "Osteoporosis," *ACOG Technical Bulletin*, No. 167 (Washington, DC: American College of Obstetricians and Gynecologists, May 1992).
5. American College of Physicians, "Clinical Guidelines—Guidelines for Counseling Postmenopausal Women About Preventive Hormone Therapy," *Annals of Internal Medicine* 117(12):1038-1041, 1992.
6. American College of Rheumatology, Council on Rheumatologic Care, *Bone Density Measurement* (position statement), (Atlanta, GA: American College of Rheumatology, March 1989).
7. Armitage, P., *Statistical Methods in Medical Research* (New York, NY: John Wiley and Sons, 1971).
8. Ashby, J., O'Hanion, M., and Buxton, M.J., "The Time Trade-Off Technique: How Do the Valuations of Breast Cancer Patients Compare to Those of Other Groups?" *Quality of Life Research* 3:257-265, 1994.
9. Australian Institute of Health, National Health Technology Advisory Panel, *Bone Mineral Assessment - An Update* (Canberra, Australia: Australian Institute of Health, October 1989).
10. Balena, R., Toolan, B.C., Shea, M., et al., "The Effects of 2-Year Treatment with the Aminobisphosphonate Alendronate on Bone Metabolism, Bone Histomorphometry, and Bone Strength in Ovariectomized Nonhuman Primates," *Journal of Clinical Investigation* 92:2577-2586, 1993.
11. Barrett-Connor, E., "Postmenopausal Estrogen and Prevention Bias," *Annals of Internal Medicine* 115(6):455-456, 1991.
12. Barrett-Connor, E., and Bush, T.L., "Estrogen and Coronary Heart Disease in Women," *Journal of the American Medical Association* 265(14):1861-1867, 1991.
13. Bass, K., Newschaffer, C., Klag, M., et al., "Plasma Lipoprotein Levels as Predictors of Cardiovascular Death in Women," *Archives of Internal Medicine* 153:2209-2216, 1993.
14. Black, D.M., *Cost Effectiveness of Screening for Osteoporosis: Review of Bone Mineral Density and Fracture Parameters Required for Model Division of Clinical Epidemiology*, University of California, San Francisco, CA, final report, Nov. 17, 1992.
15. Black, D.M., "Why Elderly Women Should be Screened and Treated to Prevent Osteoporosis," *American Journal of Medicine* 98(Suppl. 2A):67S-75S, 1995.
16. Brainsky, A., Fox, K.M., Epstein, R., et al., "The Economic Cost of Hip Fractures in the Elderly," presented at *The 41st Annual Meeting, Orthopaedic Research Society*, Orlando, FL, Feb. 13-16, 1995.

17. Browner, W.S., Pressman, A.R., Nevitt, M.C., et al., "Mortality Following Fractures in Older Women: The Study of Osteoporotic Fractures," presented at *The 4th International Symposium on Osteoporosis*, Hong Kong, 1993.
18. Bush, T.L., "Noncontraceptive Estrogen Use and Risk of Cardiovascular Disease: An Overview and Critique of the Literature," *The Menopause: Biological and Clinical Consequences of Ovarian Failure. Evolution Management*, S.G. Korenman (ed.) (Norwell, MA: Serono Symposia, USA, 1990).
19. Campodarve, I., Drinkwater, B.L., Insogna, K.L., et al., "Intranasal Salmon Calcitonin (INSC), 50-200 IU, Does Not Prevent Bone Loss in Early Postmenopausal Women," *Journal of Bone Mineral Research* 9(Suppl. 1):S391, 1994.
20. Cann, C.E., Genant, H.K., Ettinger, B., et al., "Spinal Mineral Loss in Oophorectomized Women: Determination by Quantitative Computed Tomography," *Journal of the American Medical Association* 244: 2056-2059, 1980.
21. Cauley, J.A., Cummings, S.R., Black, D.M., et al., "Prevalence and Determinants of Estrogen Replacement Therapy in Elderly Women," *American Journal of Obstetrics and Gynecology* 163:1438-1444, 1990.
22. Chapuy, M.C., Arlot, M.E., Delmas, P.D., et al., "Effect of Calcium and Cholecalciferol Treatment for Three Years on Hip Fractures in Elderly Women," *British Medical Journal* 308:1081-1082, 1994.
23. Cheung, A.P., and Wren, B.G., "A Cost-Effectiveness Analysis of Hormone Replacement Therapy in the Menopause," *Medical Journal of Australia* 156(5):312-316, 1992.
24. Christiansen, C., Christensen, M.S., McNair, P., et al., "Prevention of Early Postmenopausal Bone Loss: Controlled Two-Year Study in 315 Normal Females," *European Journal of Clinical Investigation* 10:273-279, 1980.
25. Christiansen, C., Christensen, M.S., and Transbøl, I., "Bone Mass in Postmenopausal Women After Withdrawal of Estrogen/Gestagen Replacement Therapy," *Lancet* 1:459-461, 1981.
26. Chu, J., Schweid, A.I., and Weiss, N.S., "Survival Among Women with Endometrial Cancer: A Comparison of Estrogen Users and Nonusers," *American Journal of Obstetrics and Gynecology* 143(5): 569-573, 1982.
27. Clark, A.P., and Schuttinga, J.A., "Targeted Estrogen/Progestogen Replacement Therapy for Osteoporosis: Calculation of Health Care Cost Savings," *Osteoporosis International* 2:195-200, 1992.
28. Collins, J., Donner, A., Allen, L.H., et al., "Oestrogen Use and Survival in Endometrial Cancer," *Lancet* 2(8201):961-963, 1980.
29. Copp, D.H., "Calcitonin: Discovery, Development, and Clinical Applications," *Clinical Investigation in Medicine* 17:268-277, 1994.
30. Cummings, S., "Are Patients with Hip Fractures More Osteoporotic?" *American Journal of Medicine* 78:487-494, 1985.
31. Cummings, S.R., Black, D.M., Nevitt, M.C., et al., "Appendicular Bone Density and Age Predicted Hip Fracture in Women," *Journal of the American Medical Association* 263(5):665-668, 1990.
32. Cummings, S.R., Browner, W.S., Grady, D., et al., "Should Prescription of Postmenopausal Hormone Therapy be Based on the Results of Bone Densitometry?" *Annals of Internal Medicine* 13(8):565-567, 1990.
33. Cummings, S.R., Phillips, S.L., Wheat, M.E., et al., "Recovery of Function After Hip Fracture: The Role of Social Supports," *Journal of the American Geriatrics Society* 36(9):801-806, 1988.
34. Daly, E., Roche, M., Barlow, D., et al., "HRT: An Analysis of Benefits, Risks and Costs," *British Medical Bulletin* 48(2): 368-400, 1992.

35. de Bruijn, H.P., "Functional Treatment of Colles Fracture," *Acta Orthopaedica Scandinavica* 58(Suppl. 223):1-95, 1987.
36. Deligdisch, L., and Holinka, C.F., "Endometrial Cancer: Two Diseases?" *Cancer Detection and Prevention* 10:237-246, 1987.
37. Elwood, M., and Boyes, D.A., "Clinical and Pathological Features and Survival of Endometrial Cancer Patients in Relation to Prior Use of Estrogens," *Gynecologic Oncology* 10:173-187, 1980.
38. Ettinger, B., Black, D.M., Nevitt, M.C., et al., "Contribution of Vertebral Deformities to Chronic Back Pain and Disability," *Journal of Bone and Mineral Research* 7(4):449-456, 1992.
39. Ettinger, B., and Grady, D., "Maximizing the Benefit of Estrogen Therapy for Prevention of Osteoporosis," *Menopause: The Journal of the North American Menopause Society* 1(1):19-24, 1994.
40. Ettinger, B., Selby, J., Citron, J.T., et al., "Cyclic Hormone Replacement Therapy Using Quarterly Progestin," *Obstetrics & Gynecology* 83(5 Pt 1):693-700, 1994.
41. European Foundation for Osteoporosis and Bone Disease, National Osteoporosis Foundation, and National Institute of Arthritis, Musculoskeletal, and Skin Diseases, "Consensus Development Conference: Diagnosis, Prophylaxis, and Treatment of Osteoporosis," *American Journal of Medicine* 94:646-650, 1993.
42. Felson, D.T., "Prevention of Hip Fractures," *Hospital Practice (office edition)* 23(9a):23-32, 37-38, 1988.
43. Felson, D.T., Zhang, Y., Hannan, M.T., et al., "The Effect of Postmenopausal Estrogen Therapy on Bone Density in Elderly Women," *New England Journal of Medicine* 329(16):1141-1146, 1993.
44. Finnish Academy of Science and Finnish Medical Society, "Prevention and Treatment of Osteoporosis: Summary of the Statement Prepared by the Consensus Development Conference of the Finnish Academy of Science and the Finnish Medical Society Duodecim," *Annals of Medicine* 24(3):149-151, 1992.
45. Garber, A.M., and Wagner, J.L., "Practice Guidelines and Cholesterol Policy," *Health Affairs (Millwood)* 10(2):52-66, 1991.
46. Gerard, K., Dobson, M., and Hall, J., "Framing and Labelling Effects in Health Descriptions: Quality Adjusted Life Years for Treatment of Breast Cancer," *Journal of Clinical Epidemiology* 46(1):77-84, 1993.
47. "Germany Doubts Value of Osteoporosis Screening," *Clinica* 626:7, Oct. 24, 1994.
48. Goldbloom, R., and Battista, R.N., "The Periodic Health Examination: 1. Introduction," *Canadian Medical Association Journal* 138:617-626, 1988.
49. Grady, D., Gebretsadik, T., Kerlikowske, K., et al., "Hormone Replacement Therapy and Endometrial Cancer Risk: A Meta-Analysis," *Obstetrics & Gynecology* 85(2):304-313, 1995.
50. Guccione, A.A., Felson, D.T., Anderson, J.J., et al., "The Effects of Specific Medical Conditions on the Functional Limitations of Elders in the Framingham Study," *American Journal of Public Health* 84(3):351-358, 1994.
51. Guralnik, J.M., LaCroix, A.Z., Abbott, R.D., et al., "Maintaining Mobility in Late Life," *American Journal of Epidemiology* 137(8):845-857, 1993.
52. Hall, J., Gerard, K., Salkeld, G., et al., "A Cost Utility Analysis of Mammography Screening in Australia," *Social Science and Medicine* 34(9):993-1004, 1992.
53. Harris, S.T., Watts, N.B., Jackson, R.D., et al., "Four-Year Study of Intermittent Cyclic Etidronate Treatment of Postmenopausal Osteoporosis: Three Years of Blinded Therapy Followed by One Year of Open Therapy," *American Journal of Medicine* 95:557-567, 1993.
54. Heaney, R.P., "Fluoride and Osteoporosis" (editorial), *Annals of Internal Medicine* 120(8):689-690, 1994.

55. Hillner, B.E., Hollenberg, J.P., and Pauker, S.G., "Post-Menopausal Estrogens in Prevention of Osteoporosis: Benefit Virtually Without Risk if Cardiovascular Effects are Considered," *American Journal of Medicine* 80(6):1115-1127, 1986.
56. Hui, S.L., Slemenda, C.W., and Johnston, C.C., Jr., "Baseline Measurement of Bone Mass Predicts Fracture in White Women," *Annals of Internal Medicine* 111(5): 355-361, 1989.
57. Hui, S.L., Slemenda, C.W., and Johnston, C.C., Jr., "The Contribution of Bone Loss to Postmenopausal Osteoporosis," *Osteoporosis International* 1:30-34, 1990.
58. Hui, S.L., Wiske, P.S., Norton, J.A., et al., "A Prospective Study of Change in Bone Mass with Age in Postmenopausal Women," *Journal of Chronic Disease* 35: 715-725, 1982.
59. Hunt, K., Vessey, M., McPherson, K., et al., "Long-Term Surveillance of Mortality and Cancer Incidence in Women Receiving Hormone Replacement Therapy," *British Journal of Obstetrics and Gynaecology* 94:620-635, 1987.
60. Instituto Nacional de la Salud, Ministerio de Sanidad y Consumo, *Guía Práctica de Manejo de la Osteoporosis* (Madrid, Spain: INSALUD, 1992).
61. Inzucchi, S.E., and Robbins, R.J., "Effects of Growth Hormone on Human Bone Biology," *Journal of Endocrinology and Metabolism* 79:691-694, 1994.
62. Jette, A.M., Harris, B.A., Cleary, P.D., et al., "Functional Recovery After Hip Fracture," *Archives of Physical Medicine and Rehabilitation* 68(10):735-740, 1987.
63. Jick, S.S., Walker, A.M., and Jick, H., "Estrogens, Progesterone, and Endometrial Cancer," *Epidemiology* 4(1):20-24, 1993.
64. Kamerow, D., U.S. Public Health Service Preventive Services Task Force, personal communication, February 1995.
65. Kanis, J.A., and Pitt, F.A., Epidemiology of Osteoporosis," *Bone* 13(Suppl. 1):S7-S15, 1992.
66. Kaplan, G.A., Strawbridge, W.J., Camacho, T., et al., "Factors Associated with Change in Physical Functioning in the Elderly," *Journal of Aging and Health* 51(1): 140-153, 1993.
67. Kashner, T.M., and Magaziner, J.S., "Long Term Care of Aged Hip Fractures: Public vs. Private Costs," unpublished report to the Health Care Financing Administration, University of Maryland, School of Medicine, Baltimore, MD, April 1990.
68. Kaukonen, J.P., Karaharju, E.O., Porras, M., et al., "Functional Recovery After Fractures of the Distal Forearm," *Annales Chirurgiae et Gynaecologiae* 77(1):27-31, 1988.
69. Keeler, E., and Cretin, S., "Discounting of Life-Saving and Other Non-Monetary Effects," *Managerial Science* 29:300-306, 1983.
70. Kollerup, G., Hermann, A.P., Brixen, K., et al., "Effects of Salmon Calcitonin Suppositories on Bone Mass and Turnover in Established Osteoporosis," *Calcified Tissue International* 54:12-15, 1994.
71. Kozin, S.H., and Wood, M.B., "Early Soft-Tissue Complications After Fracture of the Distal Part of the Radius," *Journal of Bone Joint Surgery* 75(A):144-153, 1993.
72. Krolner, B., and Nielsen, S.P., "Bone Mineral Content of the Lumbar Spine in Normal Osteoporotic Women: Cross-Sectional and Longitudinal Studies," *Clinical Science* 62:392-396, 1982.
73. Law, A.M., and Kelton, W.D., *Simulation Modeling and Analysis*, 2nd. Ed. (New York, NY: McGraw-Hill, Inc., 1991).
74. Lindsay, R., "Estrogen Therapy in the Prevention and Management of Osteoporosis," *American Journal of Obstetrics and Gynecology* 156:1347-1356, 1987.

75. Lindsay, R., Hart, D.M., Forrest, C., et al., "Prevention of Spinal Osteoporosis in Oophorectomised Women," *Lancet* 2(8205): 1151-1154, 1980.
76. Lindsay, R., Hart, D.M., MacLean, A., et al., "Bone Response to Termination of Oestrogen Treatment," *Lancet* 1(8708): 1325-1327, 1978.
77. MacIntyre, I., Whitehead, M., Banks, L., et al., "Calcitonin for Prevention of Postmenopausal Bone Loss," *Lancet* 1(8591): 900-902, 1988.
78. Mackillop, W.J., and Pringle, J.F., "Stage III Endometrial Cancer: A Review of 90 Cases," *Cancer* 56:2519-2523, 1985.
79. Magaziner, J., Simonsick, E.M., Kashner, T.M., et al., "Predictors of Functional Recovery One Year Following Hospital Discharge for Hip Fracture: A Prospective Study," *Journal of Gerontology* 45(3): M101-M107, 1990.
80. Magaziner, J., Simonsick, E.M., Kashner, T.M., et al., "Survival Experience of Aged Hip Fracture Patients," *American Journal of Public Health* 79(3):274-278, 1989.
81. Marottoli, R.A., Berkman, L.F., and Cooney, L.M., "Decline in Physical Function Following Hip Fracture," *Journal of the American Geriatrics Society* 40(9): 861-866, 1992.
82. Mazess, R.B., "On Aging Bone Loss," *Clinical Orthopaedics and Related Research* 165:239-252, 1982.
83. McGonigle, K.F., Karlan, B.Y., Barbuto, D.A., et al., "Development of Endometrial Cancer in Women on Estrogen and Progesterone Hormone Replacement Therapy," *Gynecologic Oncology* 55(1):126-132, 1994.
84. Melton, L.J., III, "Epidemiology of Fractures," *Osteoporosis: Etiology, Diagnosis, and Management*, B.L. Riggs and L.J. Melton, III (eds.) (New York, NY: Raven Press, 1988).
85. Melton, L.J., III, Kan, S.H., Frye, M.A., et al., "Epidemiology of Vertebral Fractures in Women," *American Journal of Epidemiology* 129(5):1000-1011, 1989.
86. Melton, L.J., III, Kan, S.H., Wahner, H.W., et al., "Lifetime Fracture Risk: An Approach to Hip Fracture Risk Assessment Based on Bone Mineral Density and Age," *Journal of Clinical Epidemiology* 41(10): 985-994, 1988.
87. Melton, L.J., III, Lane, A.W., Cooper, C., et al., "Prevalence and Incidence of Vertebral Deformities," *Osteoporosis International* 3:113-119, 1993.
88. Melton, L.J., III, and Riggs, B.L., "Epidemiology of Age-Related Fractures," *The Osteoporotic Syndrome*, L.V. Avioli (ed.) (New York, NY: Grune & Stratton, 1983).
89. Minister en de Staatssecretaris van Welzijn, Volksgezondheid en Cultuur and Minister en de Staatssecretaris van Onderwijs en Wetenschappen, *Preventie van Osteoporose: Advies Uitgebracht door de Gezondheidsraadcommissie Osteoporose*, publication no. 1991/21, (The Hague, Netherlands: Gezondheidsraad, November 1991).
90. Mossey, J.M., Mutran, E., Knott, K., et al., "Determinants of Recovery 12 Months After Hip Fracture: The Importance of Psychosocial Factors," *American Journal of Public Health* 79(3):279-286, 1989.
91. Murkies, A.L., "Common Problems with Hormone Replacement Therapy," *Australian Family and Physician* 21(3):217-225, 1992.
92. Murphy, S., Khaw, K., May, H., et al., "Milk Consumption and Bone Mineral Density in Middle Aged and Elderly Women," *British Medical Journal* 308:939-941, 1994.
93. Nachtigall, L.E., "Enhancing Patient Compliance with Hormone Replacement Therapy at Menopause," *Obstetrics & Gynecology* 75(4 Suppl.):77S-80S, 1990.
94. National Osteoporosis Foundation, "Clinical Indication for Bone Mass Measurements," *Journal of Bone and Mineral Research* 4(Suppl. 2):1-28, 1989.

95. Newton-John, H.F., and Morgan, D.B., "The Loss of Bone with Age, Osteoporosis, and Fractures," *Clinical Orthopaedics and Related Research* 71:229-252, 1970.
96. Notelovitz, M., "Hormonal Therapy in Climateric Women: Compliance and its Socio-economic Impact," *Public Health Report* 104(Suppl.):70-75, 1989.
97. O'Brien, B.J., Drummond, M.F., Labelle, R.J., et al., "In Search of Power and Significance: Issues in the Design and Analysis of Stochastic Cost-Effectiveness Studies in Health Care," *Medical Care* 32(2):150-163, 1994.
98. Orme, S.M., Simpson, M., Stewart, S.P., et al., "Comparison of Changes in Bone Mineral in Idiopathic and Secondary Osteoporosis Following Therapy with Cyclic Disodium Etidronate and High Dose Calcium Supplementation," *Clinical Endocrinology* 41:245-250, 1994.
99. Osasunerako Teknologien Ebaluaketa, *Actuación ante la Osteoporosis en el País Vasco* (Vitoria-Gastiez, Spain: OSTEBA, Departamento de Sanidad, Gobierno Vasco, June 1994).
100. Owen, R.A., Melton, L.J., Johnson, K.A., et al., "Incidence of Colles' Fracture in a North American Community," *American Journal of Public Health* 72(6):605-607, 1982.
101. Paganini-Hill, A., Ross, R.K., Henderson, B.E., et al., "Endometrial Cancer and Patterns of Use of Oestrogen Replacement Therapy: A Cohort Study," *British Journal of Cancer* 59:445-447, 1989.
102. Paganini-Hill, A., Ross, R.K., Henderson, B.E., et al., "Postmenopausal Oestrogen Treatment and Stroke: A Prospective Study," *British Medical Journal* 297: 519-522, 1988.
103. Pak, C.Y., Sakhaee, K., Piziak, V., et al., "Slow-Release Sodium Fluoride in the Management of Postmenopausal Osteoporosis," *Annals of Internal Medicine* 120(8): 625-632, 1994.
104. Petitti, D.B., Wingerd, J., Pellegrin, F., et al., "Risk of Vascular Disease in Women. Smoking, Oral Contraceptives, Noncontraceptive Estrogens, and Other Factors," *Journal of the American Medical Association* 242(11):1150-1154, 1979.
105. Pfeffer, R.I., and Van Den Noort, S., "Estrogen Use and Stroke Risk in Postmenopausal Women," *American Journal of Epidemiology* 103(5):445-456, 1976.
106. Physicians' Desk Reference, 49th Ed. (Montvale, NJ: Medical Economics Data Production Company, 1995).
107. Porter, R.W., Miller, C.G., Grainger, D., et al., "Prediction of Hip Fracture in Elderly Women: A Prospective Study," *British Medical Journal* 301(6753):638-641, 1990.
108. Potosky, A, U.S. Department of Health and Human Services, National Cancer Institute, personal communication, 1992.
109. Pstay, B., Heckbert, S., Atkins, D., et al., "A Review of the Association of Estrogens and Progestins with Cardiovascular Disease in Postmenopausal Women," *Archives of Internal Medicine* 153:1421-1427, 1993.
110. Rajan, K.T., and Evans, W.D., "Intermittent Cyclic Etidronate for Treatment of Osteoporosis," *Journal of Bone Mineral Research* 9(Suppl. 1):S269, 1994.
111. Reginster, J., "Effect of Calcitonin on Bone Mass and Fracture Rate," *American Journal of Medicine* 91(Suppl. 5B):19S-22S, 1991.
112. Reginster, J.Y., Meurmans, L., Deroisy, R., et al., "A 5-Year Controlled Randomized Study of Prevention of Postmenopausal Trabecular Bone Loss with Nasal Salmon Calcitonin and Calcium," *European Journal of Clinical Investigation* 24:565-569, 1994.
113. Robboy, S.J., and Bradley, R., "Changing Trends and Prognostic Features in Endometrial Cancer Associated with Exogenous Estrogen Therapy," *Obstetrics & Gynecology* 54(3):269-277, 1979.



114. Rosenberg, S.H., Fausone, V., and Clark, R., "The Role of Estrogens as a Risk Factor for Stroke in Postmenopausal Women," *Western Journal of Medicine* 133(4):292-296, 1980.
115. Ross, P.D., Davis, J.W., Vogel, J.M., et al., "A Critical Review of Bone Mass and the Risk of Fractures in Osteoporosis," *Calcified Tissue International* 46:149-161, 1990.
116. Ross, P.D., Wasnich, R.D., MacLean, C.J., et al., "A Model for Estimating the Potential Costs and Savings of Osteoporosis Prevention Strategies," *Bone* 9(6):337-347, 1988.
117. Rubin, G.L., Peterson, H.B., Lee, N.C., et al., "Estrogen Replacement Therapy and the Risk of Endometrial Cancer: Remaining Controversies," *American Journal of Obstetrics and Gynecology* 162(1):148-154, 1990.
118. Rubin, S.M., and Cummings, S.R., "Results of Bone Densitometry Affect Women's Decisions About Taking Measures to Prevent Fractures," *Annals of Internal Medicine* 116(12 Pt 1):990-995, 1992.
119. Sampietro-Colom, L., Almazán, C., Granados, A., *Evaluación de la Densitometría Ósea* (Barcelona, Spain: Oficina Tècnica d'Avaluació de Tecnologia Mèdica, Departament de Sanitat i Seguretat Social, Generalitat de Catalunya, 1993).
120. Sebastian, A., Harris, S.T., Ottaway, J.H., et al., "Improved Mineral Balance and Skeletal Metabolism in Postmenopausal Women Treated with Potassium Bicarbonate," *New England Journal of Medicine* 330(25):1776-1781, 1994.
121. Seeley, D.G., Browner, W.S., Nevitt, M.C., et al., "Which Fractures are Associated with Low Appendicular Bone Mass in Elderly Women?" *Annals of Internal Medicine* 115(11):837-842, 1991.
122. Seeley, D.G., Cauley, J.A., Grady, D., et al., "Is Postmenopausal Estrogen Therapy Associated with Neuromuscular Function or Falling in Elderly Women? Study of Osteoporotic Fractures Research Group," *Archives of Internal Medicine* 155(3):293-299, 1995.
123. Shapiro, S., Kelly, J.P., Rosenberg, L., et al., "Risk of Localized and Widespread Endometrial Cancer in Relation to Recent and Discontinued Use of Conjugated Estrogens," *New England Journal of Medicine* 313(16):969-972, 1985.
124. Spector, T.D., McCloskey, E.V., Doyle, D.V., et al., "Prevalence of Vertebral Fracture in Women and the Relationship with Bone Density and Symptoms: The Chingford Study," *Journal of Bone and Mineral Research* 8(7):817-822, 1993.
125. Speroff, T., Dawson, N., Speroff, L., et al., "A Risk-Benefit Analysis of Elective Bilateral Oophorectomy: Effect of Changes in Compliance with Estrogen Therapy on Outcome," *American Journal of Obstetrics and Gynecology* 164(1 Pt 1):165-174, 1991.
126. Swedish Council on Technology Assessment in Health Care (SBU), *SBU Bone Density Project. Overview & Summary of Previous Reports* (Stockholm, Sweden: SBU, April 1994).
127. Tosteson, A.N.A., Rosenthal, D.I., Melton, J., III, et al., "Cost Effectiveness of Screening Perimenopausal White Women for Osteoporosis: Bone Densitometry and Hormone Replacement Therapy," *Annals of Internal Medicine* 113(8):594-603, 1990.
128. Trent Regional Osteoporosis Working Party, *The Costs and Benefits of Screening for and Preventing Osteoporosis in Trent Region* (Trent, England: Trent Health, November 1990).
129. Tsevat, J., Goldman, L., Soukup, J.R., et al., "Stability of Time-Tradeoff Utilities in Survivors of Myocardial Infarction," *Medical Decision Making* 13:161-165, 1993.
130. "UK Government Rules Out Osteoporosis Screening," *Clinica* 641:3, Feb. 13, 1995.
131. U.S. Congress, Office of Technology Assessment, *Breast Cancer Screening for Medicare Beneficiaries: Effectiveness, Costs to Medicare and Medical Resources*

- Required—A Staff Paper* (Washington, DC: U.S. Government Printing Office, November 1987).
132. U.S. Congress, Office of Technology Assessment, *Hip Fracture Outcomes in People Age Fifty and Over—Background Paper*, OTA-BP-H-120 (Washington, DC: U.S. Government Printing Office, July 1994).
  133. U.S. Congress, Office of Technology Assessment, *Identifying Health Technologies that Work: Searching for Evidence*, OTA-H-608 (Washington, DC: U.S. Government Printing Office, September 1994).
  134. U.S. Department of Health and Human Services, Public Health Service, Food and Drug Administration, transcript of an advisory committee meeting on endocrinologic and metabolic drugs held Nov. 18, 1994, Gaithersburg, MD, transcribed by Neal R. Gross, November 1994.
  135. U.S. Department of Health and Human Services, Public Health Service, National Center for Health Services Research and Health Care Technology Assessment, "Dual Photon Absorptiometry for Measuring Bone Mineral Density," *Health Technology Assessment Reports*, No 6. (Rockville, MD: NCHSR & HCTA, 1986).
  136. U.S. Department of Health and Human Services, Public Health Service, National Center for Health Services Research and Health Care Technology Assessment, "Single Photon Absorptiometry for Measuring Bone Mineral Density," *Health Technology Assessment Reports*, No 7. (Rockville, MD: NCHSR & HCTA, 1986).
  137. U.S. Preventive Services Task Force, *Guide to Clinical Preventive Services: An Assessment of the Effectiveness of 169 Interventions*, M. Fisher (ed.) (Baltimore, MD: William & Wilkins, 1989).
  138. U.S. Public Health Service, Office of Inspector General, Office of Evaluation and Inspections, *Medication Regimens: Causes of Noncompliance*, OEI-04-89-89121 (Washington, DC: March 1990).
  139. University of Leeds, School of Public Health, and University of York, Royal College of Physicians, "Screening of Osteoporosis to Prevent Fractures," *Effective Health Care* 1:1-10, January 1992.
  140. Wasnich, R.D., Ross, P.D., Heilbrun, L.K., et al., "Prediction of Postmenopausal Fracture Risk with Use of Bone Mineral Measurements," *American Journal of Obstetrics and Gynecology* 153(7): 745-751, 1985.
  141. Weinstein, M.C., "Estrogen Use in Postmenopausal Women—Costs, Risks, and Benefits," *New England Journal of Medicine* 303(6):308-316, 1980.
  142. Weinstein, M.C., and Schiff, I., "Cost-Effectiveness of Hormone Replacement Therapy in the Menopause," *Obstetrical and Gynecological Survey* 38(8):445-455, 1983.
  143. Weinstein, R.S., Bone, H., Tucci, J., et al., "Alendronate Treatment of Osteoporosis in Elderly Women," *Journal of Bone Mineral Research* 9(Suppl. 1):S144, 1994.
  144. Weiss, N.S., "Noncontraceptive Estrogens and Abnormalities of Endometrial Proliferation," *Annals of Internal Medicine* 88: 410-412, 1978.
  145. Whitcroft, S., and Stevenson, J., "Hormone Replacement Therapy: Risks and Benefits," *Clinical Endocrinology* 36:15-20, 1992.
  146. Whitehead, M.I., Hillard, T.C., and Crook, D., "The Role and Use of Progestogens," *Obstetrics & Gynecology* 75(Suppl. 4): 9S-75S, 1990.
  147. WHO Study Group, "Assessment of Fracture Risk and Its Application to Screening for Postmenopausal Osteoporosis," *WHO Technical Report Series*, No. 843 (Geneva, Switzerland: World Health Organization, 1994).
  148. Willan, A.R., Professor of Biostatistics, McMaster University, Hamilton, Ontario, Canada, letter to the Office of Technology Assessment, U.S. Congress, Washington, DC, Jan. 11, 1995.



149. Willan, A.R., and O'Brien, B.J., "Cost-Effectiveness Ratios in Clinical Trials: From Deterministic to Stochastic Models," presented at *The American Statistical Association Meeting*, Toronto, Canada, August 1994.
150. Wilson, P.W.F., Garrison, R.J., and Castelli, W.P., "Postmenopausal Estrogen Use, Cigarette Smoking, and Cardiovascular Morbidity in Women Over 50: The Framingham Study," *New England Journal of Medicine* 313(17):1038-1043, 1985.
151. Wolman, R.L., "Osteoporosis and Exercise," *British Medical Journal* 309(6951): 399-400, 1994.
152. Woodruff, J.D., and Pickar, J.H., "Incidence of Endometrial Hyperplasia in Postmenopausal Women Taking Conjugated Estrogens (Premarin) with Medroxyprogesterone Acetate or Conjugated Estrogens Alone. The Menopause Study Group," *American Journal of Obstetrics and Gynecology* 170(5 Pt 1):1213-1223, 1994.
153. Writing Group for the PEPI Trial, "Effects of Estrogen or Estrogen/Progestin Regimens on Heart Disease Risk Factors in Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial," *Journal of the American Medical Association* 273(3): 199-208, 1995.